

Systematic review of the natural history of vestibular schwannoma

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Object. Magnetic resonance (MR) imaging now permits diagnosis of increasing numbers of small, minimally symptomatic vestibular schwannomas (VSs). Because VS growth patterns over time are very important in refining treatment strategies, these matters were systematically reviewed.

Methods. An extensive MEDLINE search was performed to cull studies on VS growth according to sequential imaging. The percentages of growing and regressing tumors and lesions requiring treatment during follow-up periods were calculated. Factors associated with differences among studies were identified. Twenty-six studies including 1340 patients met all inclusion criteria. The overall frequency of VS growth during a mean follow-up period of 38 months was 46% (95% confidence interval [CI] 43–48%) and that of regression was 8% (95% CI 6–10%). The mean annual tumor growth rate was 1.2 mm/year. Furthermore, the percentage of cases requiring treatment during follow up was 18% (95% CI 16–21%). According to results of a sensitivity analysis, evaluation by serial MR imaging (39%, 95% CI 35–43%) and a prospective study design (29%, 95% CI 21–37%) were associated with less frequent reported tumor growth.

Conclusions. Although their applicability may be limited to relatively elderly patients with small tumors, data revealing a limited frequency of VS enlargement and an infrequent necessity for eventual therapy should assist decision-making in the treatment of small VSs causing minimal symptoms.

KEY WORDS • vestibular schwannoma • tumor growth • metaanalysis • serial imaging • magnetic resonance imaging

DIAGNOSIS of VS has advanced remarkably since the clinical introduction of MR imaging. Increased use of this technology has led to the diagnosis of greater numbers of small, minimally symptomatic, or even asymptomatic, tumors. Although relatively small lesions are more amenable to either excision or stereotactic radiosurgery, the need to treat all such tumors immediately after diagnosis is controversial. Chronological growth patterns of VSs therefore are of particular interest in choosing a therapeutic modality.

Data from histopathological studies of temporal bone have demonstrated a VS incidence of 0.57 to 2.7%,^{29,31,34} whereas the clinical incidence of these neoplasms has been estimated to be one case per 100,000 patient-years (0.001%).^{16,34} This large discrepancy indicates that a majority of VSs never become symptomatic, reflecting very slow or arrested growth.

Authors of a considerable number of surgical^{27,28,41} and radiosurgical^{10–13,21} series have characterized VS. Despite the many studies on the natural history of VS and given the relatively small number of patients in each of these analyses, our understanding of the tumor's growth characteristics remains limited. In such a situation, metaanalysis permits

consideration of combined results from several smaller studies. A systematic review ensures that all useful, available data are included in a manner that minimizes selection bias. Consistency among studies concerning any finding can be tested, and causes of heterogeneity can be determined. Therefore, I performed a systematic literature review of studies concerning the natural history of VSs based on imaging data.

Clinical Material and Methods

Eligible Studies and Patients

All studies on the natural history of VSs published in English were eligible for this metaanalysis. To qualify for inclusion, each study had to provide data concerning the growth of VS as evaluated on sequential CT scanning or MR imaging. Patients who had undergone any previous treatment such as excision or stereotactic radiosurgery for the tumors were excluded. Analyses with insufficient descriptions of the follow-up period also were eliminated. Patients with neurofibromatosis Type 2 were excluded as well.

Database Search Strategy

To identify studies published up to December 2002, an extensive MEDLINE search was performed using several key words including “acoustic neurinoma (neuroma),”

Abbreviations used in this paper: CI = confidence interval; CT = computerized tomography; MR = magnetic resonance; VS = vestibular schwannoma.

TABLE 1
 Metaanalysis of 26 published clinical series including 1340 patients evaluated on sequential follow-up neuroimaging*

Authors & Year	Mean Patient Age (yrs)	Mean Tumor Size (mm)	Mean FU (mos)	No. of Patients			Annual Tumor Growth Rate (mm/yr)
				Total	w/ Tumor Growth	w/o Tumor Growth (w/ R)	
Benderson, et al., 1991	57	21	26	70	37	33 (4)	1.6
Anand, et al., 1992	56	?	64	13	2	11 (?)	?
Nedzelski, et al., 1992	68	?	42	50	24	26 (9)	1.1
Jorgensen & Pedersen, 1994	55	14	54	18	9	9 (0)	1.1
Strasnick, et al., 1994	68	10	31	51	22	29 (0)	1.1
Deen, et al., 1996	67	12	41	68	20	48 (?)	0.7
Glasscock, et al., 1997	75	8	29	34	19	15 (0)	2.9
Yamamoto, et al., 1998	58	?	20	12	7	5 (0)	?
Modugno, et al., 1999	60	11	36	47	17	30 (?)	1.4
Niemczyk, et al., 1999	60	?	6	15	7	8 (?)	?
Charabi, et al., 2000	59	8	50	127	108	19 (8)	?
Luetje, 2000	65	14	46	47	13	34 (6)	?
Massick, et al., 2000	75	9	47	15	9	6 (1)	?
Mirz, et al., 2000	55	11	43	64	15	49 (14)	0.4
O'Reilly, et al., 2000	64	?	31	43	12	31 (0)	?
Rosenberg, 2000	70	10	53	80	46	34 (6)	0.9
Shin, et al., 2000	63	12	31	87	46	41 (10)	1.5
Tschudi, et al., 2000	52	16	35	74	23	51 (8)	0.7
Walsh, et al., 2000	61	9	40	72	26	46 (10)	1.2
Hoistad, et al., 2001	64	9	29	102	45	57 (3)	1.0
Nutik & Babb, 2001	62	5	42	75	31	44 (?)	1.3
Perry, et al., 2001	71	11	42	41	21	20 (1)	1.7
Sakamoto, et al., 2001	57	17	33	31	14	17 (3)	2.4
Stipkovits, et al., 2001	58	?	42	44	8	36 (3)	?
Nader, et al., 2002	52	13	42	22	11	11 (?)	?
Vokurka, et al., 2002	62	10	12	38	19	19 (2)	?

* FU = follow up; R = regression; ? = unknown.

“vestibular schwannoma,” and “natural history” in appropriate combinations. From among more than 4000 studies listed, articles on the growth of VSs were identified. Reference lists in all papers retrieved were examined to find additional studies. In turn, reference lists in articles thus found were checked to identify still more studies. When two or more studies originated from a single institution, overlap of study populations was avoided by using only the most recent publication, which usually included the largest number of patients and the longest follow-up periods.

Data Extraction

Data extracted from the studies included year of publication; study design (prospective or other); number of patients; age of patients; duration of follow up; imaging modality (MR imaging alone compared with CT scanning or MR imaging); initial tumor diameter; tumors showing growth, no growth, or regression during the follow-up period; annual growth rate of tumors; and the need for eventual treatment during the follow up and the modality used (excision or radiosurgery).

Tumor size was expressed in different ways in the various studies. Although a volumetric calculation obtained using a mathematical formula is likely to be the most accurate, tumor diameter was reported more frequently than was tumor volume. Therefore, in the current study tumor size was expressed as tumor diameter, despite the fact that lesion diameter was defined in different ways in individual stud-

ies such as maximal diameter or the mean diameters of the x- and y-axes on the neuroimage. Annual tumor growth rate was calculated by dividing the change in lesion diameter by the follow-up period (mm/year).

Data Analysis

The percentage of tumors that had grown during follow up was calculated for each study separately as well as for all studies combined. The number of patients per study was used as a weighing factor, so that larger studies would have more impact than smaller ones. Heterogeneity among studies was assessed using a chi-square test to determine whether the variability of study-specific estimates of tumor growth frequency was greater than that expected from sampling error alone. An estimate of tumor growth frequency across studies together with a 95% CI was calculated using the Mantel-Haenszel method. The following variables also were obtained across studies, by calculation when possible: patient age, initial tumor diameter, and duration of follow up. Authors of most studies stated the number of tumors that had regressed; an overall regression rate from these articles was calculated as a percentage. Finally, we calculated the percentage of all tumors requiring treatment during the observation period.

The influence of the following variables on the likelihood of tumor growth was evaluated: study design (prospective compared with other), imaging modality (MR imaging alone compared with CT or MR imaging), publication year,

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patient age, tumor size, and duration of follow up. Sensitivity analysis was performed using simple and multiple logistic regressions to identify factors associated with differences among studies. The median value of each continuous variable across studies was used as a cut-off point, and the difference in tumor growth frequency between cases above and those below the median value for each variable was assessed. A probability value less than 0.05 indicated statistical significance. All statistical calculations were performed using a personal computer running a statistical software package (SPSS, version 11.0; SPSS Japan, Tokyo, Japan).

Results

Characteristics of Studies, Patients, and Tumors

Twenty-six studies with 1340 patients (12–127 patients per study) met all inclusion criteria (Table 1).^{1,2,4,5,7–9,14–20,22–26,30,32,33,35,37,38,40} The publication year ranged from 1991 to 2002. Only four studies were prospective,^{15,16,32,40} and the other 22 were retrospective or unspecified. The mean follow-up period was 38 months (range 6–64 months). Tumor growth was evaluated on serial MR imaging in 12 studies,^{8,15,17,20,23,24,26,32,35,37,38,40} on CT or MR imaging in the other 14.^{1,2,4,5,7,9,14,16,18,19,22,25,30,33} The mean age of patients was 62 years (range 52–75 years). Information regarding initial tumor size was available in 22 studies (1163 patients). The mean tumor diameter in the various studies was 11 mm (range 5–21 mm).

Tumor Growth and Subsequent Treatment

The frequency of tumor enlargement over time varied from 15 to 85% in the individual studies, rates that were statistically heterogeneous. The overall frequency of tumor growth during the follow-up period was 46% (95% CI 43–48%; Table 2). Authors of 20 studies including 1100 patients reported the number of patients whose tumors showed regression. The estimated frequency of tumor regression based on these studies was 8% (95% CI 6–10%). The annual tumor growth rate was described in 16 studies including 964 patients and was a mean 1.2 mm/year (range 0.4–2.9 mm/year).

Nineteen studies (930 patients) contained information concerning therapy needed in patients who initially had been treated conservatively through the use of serial imaging. At the end of the follow-up period, 760 patients were still under observation. The remaining 170 underwent treatment because of tumor enlargement or clinical deterioration at various time points; 131 had surgery, whereas 39 underwent radiosurgery. The estimated percent of treatment required during the follow-up period was 18% (95% CI 16–21%), involving microsurgery in 14% (95% CI 12–16%) and radiosurgery in 4% (95% CI 3–5%).

Sensitivity Analyses

Univariate and multivariate sensitivity analyses were performed to consider associations between differences in tumor growth frequency among studies and the following factors: study design, imaging modality, publication year, patient age, tumor size, and duration of follow up (Table 3). Results of simple logistic regression demonstrated no significant relationship between tumor growth frequency and

TABLE 2
Summary of combined data and data availability in literature review of VS studies

Variable	Value (95% CI)	Data Availability	
		No. of Studies	No. of Patients
mean patient age (yrs)	62	26	1340
mean follow-up period (mos)	38	26	1340
mean initial tumor size (mm)	11	20	1163
tumor enlargement rate (%)			
all studies	46 (43–48)	26	1340
MRI studies	39 (35–43)	12	534
prospective studies	29 (21–37)	4	135
tumor regression rate (%)	8 (6–10)	20	1100
annual tumor growth rate (mm/yr)	1.2	16	964
subsequent treatment rate (%)	18 (16–21)	19	930
microsurgery	14 (12–16)		
radiosurgery	4 (3–5)		

year of publication, patient age at diagnosis, or duration of follow-up period. Study design and imaging modality correlated with tumor growth frequency on univariate analysis; specifically, prospective design and evaluation through serial MR imaging were significantly associated with lower tumor growth frequency. Results of multiple logistic regression performed to adjust for potential confounding variables confirmed these data. Larger tumors also were associated with a lower risk of VS enlargement.

Subgroup Analysis of High-Quality Studies

Considering the results of the sensitivity analysis, a subgroup analysis was performed in which only high-quality studies were examined. In the 12 studies in which MR imaging was the only imaging modality used, the frequency of tumor enlargement was calculated to be 39% (95% CI 35–43%; Table 2) during 33 months of follow up. Furthermore, if analysis was confined to the cases in the four studies with a prospective design, the mean follow-up period was 41 months and the estimated tumor growth frequency was 29% (95% CI 21–37%).

Discussion

Advances in imaging modalities now permit longitudinal studies detailing the natural history of VS growth. Although slow growth is considered characteristic of these tumors, the growth rate may be irregular, even in a single tumor. Some lesions enlarge rapidly, whereas the size of others remains stable or even regresses. Furthermore, observed tumor enlargement does not necessarily indicate a need for treatment. Several growth patterns have been identified: stability, initial growth followed by stability, stability followed by regression, continuous regression, and continuous growth.³⁵ Therefore, controversy exists concerning the timing of therapy to minimize morbidity and death while maximizing quality of life.

TABLE 3
Sensitivity analysis of 26 studies on VS enlargement*

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
study design (prospective compared w/ other)	0.45 (0.31–0.66)	0.50 (0.37–0.67)
imaging modality (MRI only compared w/ CT & MRI)	0.64 (0.51–0.80)	0.41 (0.24–0.71)
yr of publication (2000 & after compared w/ 1999 & before)	1.13 (0.89–1.44)	0.67 (0.49–0.92)
mean patient age (≥ 62 yrs compared w/ ≤ 61 yrs)	0.93 (0.75–1.15)	0.59 (0.46–0.77)
mean tumor diameter (≥ 11 mm compared w/ ≤ 10 mm)	0.55 (0.43–0.69)	0.52 (0.40–0.68)
mean duration of FU (≥ 39 mos compared w/ ≤ 38 mos)	1.10 (0.88–1.36)	0.80 (0.60–1.07)

* OR = odds ratio.

The management of VS continues to evolve. Once a high-morbidity procedure, surgical removal now involves fewer problems with cranial nerve deficits and shows great improvement in postoperative functional status.^{27,28} On the other hand, stereotactic radiosurgery has become an alternative to microsurgery. In recent reports, 49 to 62% of VSs decreased in size after stereotactic radiosurgery, with 33 to 43% remaining the same and 0 to 9% showing enlargement subsequently.^{10–13,21} Data from these studies clearly demonstrate that the percentage of VSs that continue to grow is reduced by radiosurgery. Nevertheless, both microsurgery and radiosurgery carry potential risks in patients, including loss of hearing and vestibular function, facial nerve palsy, brainstem edema or infarction, and cerebrospinal fluid leakage associated with meningitis. Several authors have reported that risks associated with microsurgery and radiosurgery, which include both functional and psychological morbidity as well as death, often are underestimated.^{3,9,36,39}

A third treatment option consists of observation through serial imaging studies, which seems the best option for select patients. One may question whether the benefits of early intervention outweigh any risks that might indicate a more conservative initial strategy. More than half of the patients treated through observation did not show tumor enlargement, and fewer than one fifth required therapy during an observation period of 3 years, thus indicating that most patients with VS do not require intervention. Nevertheless, 3 years represents a relatively short duration of follow up, and this limited period must be taken into account. With continuing advances in imaging procedures, smaller tumors are being detected in patients with fewer symptoms. This trend is important in determining whether all tumors must be treated immediately after diagnosis or alternatively followed until intervention is indicated by a combination of tumor growth and occurrence of symptoms. It is obvious that treatment results are related to tumor size. Therefore, patients who undergo intervention following conservative management may have a higher risk of tumor enlargement than they would at an earlier time. Whether outcome is adversely affected by the treatment delay should be carefully evaluated.

The present study has several limitations that require caution in the interpretation of its data. First, systematic reviews may fail to include all relevant studies, especially unpublished ones. Because 26 studies were identified, one would expect the effect of a small number of missing studies to be small. Publication bias is an important consideration because novel or surprising results may be favored for publication.⁶ Although reports of microsurgical or radiosur-

gical results tend to reflect significant publication bias,⁴² one would not expect the rate of tumor growth in follow-up studies of VS to have a great effect on the likelihood of publication.

Second, the analyzed data here cannot predict the natural history of VS in patients of all ages with tumors of all sizes. Obviously, the data collected in this study was associated with significant bias, thus limiting their applicability to the general population of patients with VS. In particular, relatively young patients harboring large tumors with brainstem compression typically are treated using surgery, whereas young or middle-aged patients with small or medium-sized tumors often undergo radiosurgery. In contrast, relatively elderly patients with small tumors have been given trials of observation through serial imaging to follow tumor growth; accordingly, these patients predominate in the current meta-analysis. The mean patient age in the current study, 62 years, is older than those in most studies of patients undergoing surgery or radiosurgery.^{10–13,21,27,28} Thus, data in the present study provide little information about the growth rate of large VSs in young patients. The applicability of the results may be limited to relatively elderly patients with small tumors.

Third, the percent of tumors that enlarged over time varied from 15 to 85% in individual studies. Note that the results of these studies proved to be heterogeneous, thus indicating that differences between the studies were unlikely to have arisen from sampling error alone. This diversity of results may be explained by one or more factors: clinical material selected (patient age, tumor size, and so forth), limited numbers of patients, different observation periods, and different neuroradiological modalities used to detect and estimate lesion growth. Sensitivity analysis, performed to examine possible causes for heterogeneity between studies, revealed a statistical association between tumor growth frequency and factors indicative of a high-quality study, that is, a prospective design and evaluation through MR imaging. Specifically, the calculated tumor growth rate based on data from studies selected for high quality was somewhat lower than the overall percentage. Perhaps these results indicate that actual tumor growth may be less frequent than demonstrated by the overall results of this metaanalysis.

Fourth, smaller tumors were associated with higher risks of enlargement. The reason is unclear and the result may have been influenced by the bias that small tumors predominate in most studies. Perhaps radiological evaluation of tumor enlargement is more sensitive in smaller tumors than in larger ones. It is difficult to identify a threshold size below which lesion growth is less likely.

Conclusions

In summary, a 46% overall estimated frequency of VS enlargement and an 18% rate of eventual treatment after conservative management may offer guidance in clinical decision-making in the treatment of small VSs causing minimal symptoms.

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