Clinical Predictors Leading to Change of Initial Conservative Treatment of 836 Vestibular Schwannomas

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Abstract

Objective This study was aimed to determine the role of clinical presentation and tumor characteristics in vestibular schwannoma (VS) at diagnosis, initially treated with conservative management.

Design The study was designed as a retrospective chart review.

Setting The study was prepared at national tertiary referral center for VS patients.

Participants A total of 836 VS patients, initially treated conservatively, were included.

Main Outcome Measures Patient characteristics: age at diagnosis, gender, frequency, and duration of, hearing loss, tinnitus, balance disorder (unsteadiness, dizziness, and vertigo), respectively; and tumor characteristics: laterality, growth, cystic component, and location were analyzed in relation to tumor size at diagnosis and change in treatment strategy.

Results In total, 169 (20%) patients had a change in treatment strategy. Factors at diagnosis that had a high influence on intervention were a short duration of hearing loss (hazard ratio [HR]: 4.8, $p < 0.001$) and cystic tumors (HR = 2.6, $p < 0.001$). Balance disorders and extracanalicular (EC) tumor location have a medium influence on intervention (HR = 1.6, $p < 0.01$). Tumour growth was seen in 55% of the intervention group; we found a significant correlation with a short duration of hearing loss. Cystic VS was significantly higher between the medium and large tumors, 24.3% and 38.1%. ($p = 0.001$), respectively.

Conclusions Patients with a short duration of hearing loss, balance disorders, EC located tumors, and cystic tumors have a significantly higher chance of a change in treatment strategy. Large tumor size at diagnosis and a cystic component were related to age > 65 years at diagnosis.

Keywords

- ▶ acoustic neuroma
- ▶ conservative treatment
- ▶ magnetic resonance imaging
- ▶ sensorineural hearing loss
- ▶ decision making
- ▶ risk factors

Introduction

Vestibular schwannoma (VS), a benign tumor, accounts for 80 to 90% of the tumors found in the cerebellopontine area.^{1,2} Incidence in the Netherlands is assumed to be 1.6 per 100,000 persons a year, based on several Danish studies.^{3–6} The incidence has increased over the years, probably due to the wide availability of advancing magnetic resonance ima-

ging (MRI) techniques, as well as higher awareness among doctors and patients.

The mean age at diagnosis has slowly been rising over the past 40 years to a mean age at diagnosis of 58 years, although the size of VS at diagnosis has decreased, from a mean size of approximately 30 mm in the 1970s to 10 mm, measured, in the beginning of the 20th century.^{4,5}

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With regard to diagnosing VS, the clinical presentation is of importance, comprising hearing loss, tinnitus, and balance disorder. Unfortunately, the symptomology varies exceedingly.^{6,7}

Apart from active treatment, radiation therapy and microsurgery, the mainstay is usually conservative management which includes regular MRI. Active treatment can result in increased hearing loss, balance disorder, facial nerve damage, and other cranial nerve deficits.^{6,8} When tumor size exceeds 20 mm or tumor growth is > 2 mm/year, the need for active treatment is usually apparent.⁹ With small or medium-sized tumors, the decision for treatment is often a matter of debate.^{4,6,10} Although a conservative approach to the treatment for VS has become increasingly accepted, an optimal treatment strategy and timing is not yet available.^{2,11} In the literature, Stangerup and Caye-Thomasen stated that all extracanalicular VS > 20 mm should be treated.⁴ Timmer et al concluded that unsteadiness and a short duration of hearing loss strongly predict tumor growth.¹² To determine a more optimal treatment, both tumor characteristics and the patient's characteristics and preferences have to be considered.^{3,13,14}

The main objective of this study was to investigate the relationship among age, symptoms, and tumor size at diagnosis and the duration of conservative management, in an initially large conservatively treated group.

Material and Methods

Since 2002 the Leiden University Medical Center (LUMC) has maintained a skull-base database, consisting of VS patients nationally referred to the LUMC. This database is the result of a weekly multidisciplinary meeting comprising clinical presentation, radiologic tumor information, and treatment advice for each patient. Advice ranges from intervention to conservative approach. When the advice is conservative, it consists of follow-up MRI at 3, 6, or 12 months. This interval is the result of a combination of clinical information and radiologic tumor information. For example, a medium-sized, cystic tumor is followed-up with MRI after 3 months, whereas an intracanalicular tumor, with no useful hearing, is followed-up after 12 months. Radiologic tumor information is obtained from MRI performed in the referring hospital and during wait and scan protocol; the results consist of images, report, or both.

Study Design

A retrospective chart review was conducted of VS patients diagnosed in the period from 2002 until 2012; they were initially treated with conservative management. All patients were diagnosed with VS by means of MRI, initially conservative management and a follow-up MRI scan. Patients diagnosed with neurofibromatosis type 2 (NF2) were excluded.

Clinical Presentation at Diagnosis

Data regarding patient and tumor characteristics were obtained for each patient. Patients' characteristics collected at diagnosis were: age, gender, hearing classification, tinnitus, and balance disorders. Balance disorders, in accordance with disability, where subdivided into three groups, from low to high: unsteadiness, dizziness, and vertigo. Tumor characteristics collected at diagnosis were tumor size, location, growth, and homogeneity (cystic component). Presence as well as duration of the complaints at diagnosis was admitted in the database. For duration measurements, we used 5-year intervals.

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Hearing Classification

Hearing was classified according to the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) guidelines.⁹ The combination of pure tone average (PTA) and speech discrimination (SD) was used to measure hearing, as shown in ►Fig. 1.

PTA was calculated as the mean of the hearing capacity in decibel (dB) at frequencies of 500 HZ, 1,000 HZ, 2,000 HZ, and 4,000 HZ. SD was measured as the maximum percentage of words correctly identified at an easily detectable intensity level. Classes A and B are defined as useful hearing.

Age at Diagnosis

Age at diagnosis was divided into three age groups: < 55 years, 55 to 65 years, > 65 years.

Tumour Characteristics at Diagnosis

Tumour size was registered according to internationally accepted Kanzaki's classification and is measured by either intracanalicular (IC) or extracanalicular (EC) result.⁹ This means that in the axial plan on a T1 gadolinium-enhanced sequence, the largest diameter was measured in anterior-posterior and medial-lateral dimension. Tumours were categorized in four size groups, respectively: IC and 3 subgroups of EC, < 11 mm, 11 to 20 mm, and > 20 mm. Tumour size was measured using axial MRI, T1-weighted sequences enhanced with gadolinium or T2-weighted sequence and the largest diameter.

Besides tumor size, the side and homogeneity (cystic component) of the tumor was noted. The tumor was defined as cystic, when a cystic component was present.

Fig. 1 Nomogram of the hearing classification. Horizontal: speech discrimination in %. Vertical: mean hearing loss in 500/1000/2000/4000 HZ in decibel (dB). Class A: normal hearing, class D: not useful hearing.

Clinical Outcome

The main outcome of measurement was a change in treatment strategy. Depending on information from referral hospitals, an attempt was made to assess tumor growth during follow-up. Growth was defined as > 2 mm/year.¹³

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0. Categorical data was made by using Chi-square test correlations. The correlation was considered significant at a p -value of < 0.05 . Cox's proportional hazard analysis was used to create a hazard ratio (HR), using years of follow-up and the presence of an intervention.

Results

Between 2002 and 2012, 1,433 patients with vestibular schwannomas were discussed in the multidisciplinary skull base meeting. Of these, 597 patients were excluded because of directly active treatment (i.e., radiotherapy or microsurgery) or NF2. Eight hundred and thirty-six patients were followed initially with conservative management (► Fig. 2). Ninety-eight patients were lost to follow-up; data for 738 patients concerning the presence or absence of an intervention were available.

Patient Characteristics and Clinical Presentation

► Table 1 shows patient characteristics. Between different age groups, there was no significant difference number of these groups; < 55 (33%), 55 to 65 (32%), > 65 (34%). Mean age at diagnosis was 59.7 year (SD = 11.6). Patients older than 65 years had significantly larger tumor size at diagnosis (76%, $p = 0.005$).

Hearing loss (96%) and tinnitus (69%) were the most reported complaint at diagnosis. Balance disorders were seen in almost half of the patients, in detail, unsteadiness (33%), dizziness (7%), and vertigo (9%).

Fig. 2 Inclusion flowchart of VS patients initially treated conservatively. NF2: neurofibromatosis type 2; VS: vestibular schwannoma.

All complaints were relatively equally distributed among different tumor sizes at diagnosis, and no significant relationships were found between frequency of complaints and tumor size.

Hearing Classification

The pure tone audiometry at diagnosis was applicable for 707 (85%) patients, with a mean maximal speech recognition of 73.5 (SD = 30.9), shown in ► Table 2. Fifty-one percent of the patients had useful hearing at diagnosis, whereas 20% of patients had a category D hearing score. There was no correlation between hearing loss and tumor size at diagnosis.

Tumour Characteristics

The tumor sizes at diagnosis for all VS wait-and-scan patients were divided into IC and EC located tumors. Of all tumors, 421 (50%) were located IC at diagnosis.

Of the 415 EC tumors, 217 were < 11 mm, 177 were between 11 and 20 mm and 21 tumors were > 20 mm. The tumor side was almost equally distributed, 399 (48%) were right sided and 437 (52%) were left sided. In 11% of all VS, a cystic component was found. Cystic VS is significantly higher between the medium and large tumors, 24.3% and 38.1% ($p = 0.001$), respectively. In total, most tumors with a cystic component (49%) were found in medium-sized tumors at diagnosis.

Clinical Outcome: Change in Treatment Strategy

Of 738 conservatively treated patients, 169 (23%) patients had an intervention (► Table 3). The mean follow-up of conservatively treated patients was 3.4 years (SD = 2.1). The mean follow-up, before treatment, among patients who received intervention was 2.19 years (SD = 1.4). We found a significant correlation between intervention and balance disorders (42%, $p = 0.007$), duration of hearing loss < 1 year (61%, $p < 0.0001$), EC located tumors (62%, $p < 0.001$), and a cystic tumor component (23% $p < 0.0001$). The data were analyzed by a Cox's proportional hazard analysis. This showed a high HR for short duration hearing loss (HR = 4.6, $p < 0.001$) and cystic tumors (HR = 2.06, $p < 0.001$). Balance disorders and EC tumor location had a medium HR for intervention (HR = 1.6, $p < 0.01$).

Clinical Outcome: Growth

Tumour growth was defined for the intervention group only, due to inconsistent data in the remaining group. Growth (> 2 mm/year) was seen in 92 patients (54%), ► Table 4. Within this group, we found a significant correlation with a short duration of hearing loss (HR = 3.5, $p < 0.044$) and a nearly significant correlation with cystic tumors and EC located tumors (HR = 1.5, $p = 0.088/0.094$; ► Table 5).

Clinical Outcome: Predictive Value of Tumor Size at Diagnosis

► Table 1 shows that there was no significant relationship among gender, tumor side, frequency of symptoms, audiometry, and tumor size at diagnosis.

Patient factors that significantly influenced tumor size at diagnosis were cystic tumors and age at diagnosis (when categorized in groups), and 76% of tumors > 20 mm were

Table 1 Patient characteristics

		Total	Tumor size at diagnosis			
			IC	< 11mm	11–20 mm	> 20 mm
Number of patients		836	421	217	177	21
Gender	Male	434	222	102	99	11
	Female	402	199	115	78	10
Age in groups (y)	< 55	280	137	76	65	2
	55–65	269	139	74	53	3
	> 65	287	145	67	59	16 ^a
Cystic		88	11	26	43	8 ^a
Side	right	399	205	102	83	9
	left	437	216	115	94	12
Mean age at diagnosis (y)		59	59	58	59	69
Frequent of symptoms						
– Hearing loss		800	401	209	170	20
– Tinnitus		575	305	147	115	8
– Unsteadiness		273	149	70	47	7
– Dizziness		55	29	14	12	0
– Vertigo		79	35	21	20	3
Mean follow-up (y)		3.4	3.5	3.1	3.1	3
Lost to follow-up		98				
Intervention	yes	169	65	60	38	6 ^a
	no	569	300	138	119	12
Kind of intervention	RT	62	23	22	16	1
	MS	107	42	38	22	5

Abbreviations: IC, intracanalicular; MS, microsurgery; RT, radiotherapy.

^aStatistically significant ($p < 0.05$).**Table 2** Hearing classification

Hearing classification	Total	Tumor size at diagnosis			
		IC	< 11 mm	11–20 mm	> 20 mm
	707				
A	151	78	44	28	1
B	211	113	50	44	4
C	210	94	63	48	5
D	135	66	32	29	8

Abbreviation: IC, intracanalicular.

found among patients older than 65 years ($p = 0.005$). Cystic VS is found in 38.1% of large tumors ($p = 0.001$).

No relationship was found between different intervention methods and tumor size.

Discussion

This study investigated correlations among tumor size at diagnosis, tumor characteristics, clinical presentation, the duration of follow-up and change in treatment strategy. The main findings were that patients with a short duration of

Table 3 Intervention

		Total	Intervention	
			Yes	No
		738	169	569
Tumor location	IC	368	65	303
	EC	370	104 ^a	266
Cystic		78	39	39
Balance disorders		249	73 ^a	176
Duration hearing loss	< 1	293	98 ^a	195
	1–5	218	45	173
	5–10	69	11	58
	> 10	74	7	67

Abbreviations: IC, intracanalicular; EC, extracanalicular.

^aStatistically significant.

hearing loss, balance disorders, EC located tumors, and cystic tumors have a significantly higher chance of change in treatment strategy. Large tumor size at diagnosis and a cystic component are related to age > 65 years at diagnosis.

Conservative treatment has been accepted management for VS for many years. Multiple potential factors have been

Table 4 Patients with growth and tumor characteristics

			Total
Growth > 2 mm/y			92
Patient characteristics	Age at diagnosis in y (mean)		58.61
	Age groups	30–50	23
		50–70	52
		70–90	17
	Gender	Male	41
		Female	51
Tumor characteristics	Tumor location	IC	33
		EC	59
	Size	< 11 mm:	70
		11–20 mm:	19
	Side	> 20 mm	3
		Right	47
		Left	45
	Cystic	Yes	25
		No	67

investigated but the realization of usable tumor growth prediction models persists. By reviewing the literature and comparing it with the data of the current study, the following points are addressed below.

In the literature, tumor size is a solid factor on which to support treatment strategy, except for medium-sized tumors. In this group, it is often a matter of debate, whether active or conservative treatment is more appropriate. Com-

paring these data with the Danish, they recommend primary treatment for tumors larger than 15 to 20 mm at diagnosis and for tumors with a cystic component.⁴ In the database of current study, 421 (50%) of conservatively treated VS are IC, 21 (3%) are larger than 20 mm, and 177 are between 11 and 20 mm. Because of the significant relationship between cystic and large tumors, our advice is to treat, and this advice is in line with Stangerup and Caye-Thomasen.⁴ Cystic tumor components have an enhanced chance of intervention; therefore, primary treatment should be considered at diagnosis or the interval of follow-up MRI should be shortened. In medium-sized tumors, this study differs from the Danish and suggest an initially conservative treatment. In this study, 22.5% of medium-sized tumors had intervention.

Numerous studies have predicted symptoms at diagnosis as a possible predictor of tumor behavior and change-in-treatment strategy. Timmer et al analyzed 240 conservatively treated VS patients, this group found a relation between complaints and tumor location at diagnosis and tumor growth. They suggested that tumor location, a short duration of hearing loss, unsteadiness, and sudden deafness as the best variables in predicting tumor growth.^{12,15} Jethanamest et al stated that disequilibrium, imbalance or both at diagnosis might be associated with significant tumor growth.¹⁶ Current practice by lead authors of this paper found that tumor location, a short duration of hearing loss, and balance disorders, among other factors, are presumed to be the best factors in predicting changes in an initially conservative treatment strategy. Furthermore, patients with a short duration of hearing loss had an almost 3.5 times of higher chance of intervention than a longer duration of hearing loss. Considering the group with growth > 2 mm, 52 patients (55%) had balance disorders, this was not a significant difference. Due to inconsistency of data regarding tumor

Table 5 Cox proportional hazard analysis

Change in treatment strategy (events <i>n</i> = 148, censored <i>n</i> = 441)					Tumor growth > 2 mm (events <i>n</i> = 84, censored <i>n</i> = 61)			
			95% CI for Exp. (B)				95% CI for Exp.(B)	
	Exp. (B) HR	Sig.	Lower	Upper	Exp. (B) HR	Sig.	Lower	Upper
Age	1.227	0.248	0.867	1,738	1,479	0.114	0.910	2,405
Audiometry		0.000				0.025		
Audiometry class A	0.360	0.000	0.209	0.621	0.392	0.011	0.190	0,806
Audiometry class B	0.514	0.003	0.331	0.798	0.486	0.015	0.272	0,868
Audiometry class C	0.421	0.000	0.263	0.673	0.454	0.020	0.234	0,884
Hearing loss		0.000				0.187		
Hearing loss < 1 y	4,758	0.000	2,178	10,395	3,493	0.045	1,025	11,899
Hearing loss 1–5 y	2,571	0.022	1,145	5,773	3,470	0.054	0.980	12,288
Hearing loss 5–10 y	1,744	0.261	0.662	4,598	2,072	0.351	0.448	9,583
Balance disorders	1,563	0.010	1,113	2,195	1,583	0.077	0.955	2,478
Cystic tumor	2,557	0.000	1,708	3,827	1,492	0.146	0.870	2,561
Tumor location	1,581	0.011	1,110	2,251	1,418	0.159	0.872	2,304

Abbreviations: CI, confidence interval; Exp., expected; HR, hazard ratio; Sig., significant.

Note: in the audiometry section group D was used as reference and for hearing loss, group > 10 years.

growth, this study cannot make a clear pronouncement of whether there is a direct connection between intervention and tumor growth. In total, 169 patients underwent intervention, and 92 (55%) had > 2 mm of growth.

Kentala et al studied the influence of clinical presentation at diagnosis of tumor size in detail before. They examined the clinical presentation of 122 patients with VS and concluded that hearing loss (94%, $n = 115$) and tinnitus in (83%, $n = 101$) were the most reported complaints. However, tumor size did not correlate with any of these complaints at diagnosis.⁷ Current study found a similar ratio of complaints among our 836 conservatively treated patients and, accordingly, there were no significant relationships with tumor size at diagnosis or growth.

The change of the initial management strategy for 169 (23%) patients depended on multiple factors corresponding to tumor growth, increasing complaints and patient preference. The discrepancy between no tumor growth and intervention is in current practice by lead authors of this paper due to the fact that patients' preference and increasing complaints is sometimes stronger than tumor growth alone, despite extensive counseling. Therefore, intervention was not the most objective outcome measurement. On the other hand, if conservative management needs adjustment, it does reflect on possible criteria that determine the most suitable strategy. Change in treatment strategy has been used as outcome measurement before.^{16–18} Jethanamest et al evaluated conservatively treated patients and found that 22.3% of patients underwent change from an initially conservative management,¹⁶ similar to these results (23%). A prospective study performed by Hajioff et al reported a 35% change in initially conservative management. They found no correlation among clinical presentation, tumor size, and a change in management.¹⁸ However, they did not study balance disorders, duration of symptoms, tumor characteristics, and tumor location.

Our results state a very clearly significant relationship between these criteria at diagnosis and intervention later on. The reason for intervention was based on multiple factors where tumor factors, increasing complaints, and patients' preferences were considered, this was done on a case-by-case basis. With this in consideration, the literature and the physician's experience play an important role.

To our knowledge, with 836 VS patients, this is one of the largest retrospective studies performed on VS patients who were initially managed conservatively. Being aware of the drawback of this retrospective study, it cannot make clear pronouncements. Nevertheless, this study contains one of the largest number of patients so far and provide us interesting data of patient and tumor characteristics at diagnosis which lead to change of treatment strategy.

For future studies, the only way to succeed in predicting tumor behavior is to optimize data collection according to a strict format. At location, information is gathered using the same methods, and MRI scanning is performed according to a similar protocol. With this in mind, a prospective study, focusing on the patient and tumor factors as described, will have the best chance of predicting VS behavior in the

future. Predicting tumor behavior results in better counseling and MRI intervals, and different treatment strategies become accessible. The on-going process of optimizing imaging in VS, regarding perfusion MRI and predicting growth, is in our opinion, important for future decision making.¹³

In summary, this study shows that patient and tumor characteristics influence tumor size at diagnosis and intervention later on. In our opinion, conservative management is treatment modality number one, except for large cystic VS. The interval of MRI follow-up should be based on tumor and patient characteristics. For example, a 65-year-old person with a large cystic tumor has an MRI interval of 6 months instead of a year. In this way, different treatment modalities stay optional and surgical outcome is beneficial, meaning better facial nerve outcomes, and completeness of resection.¹⁹ Patients' characteristics that are significant are short duration of hearing loss and balance disorders. Tumor characteristics that are significant are extrameatal and cystic tumors.

Conflict of Interest

None.

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