Conservative Management or Gamma Knife Radiosurgery for Vestibular Schwannoma: Tumor Growth, Symptoms, and Quality of Life

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BACKGROUND: There are few reports about the course of vestibular schwannoma (VS) patients following gamma knife radiosurgery (GKRS) compared with the course following conservative management (CM). In this study, we present prospectively collected data of 237 patients with unilateral VS extending outside the internal acoustic canal who received either GKRS (113) or CM (124).

OBJECTIVE: The aim was to measure the effect of GKRS compared with the natural course on tumor growth rate and hearing loss. Secondary end points were post-inclusion additional treatment, quality of life (QoL), and symptom development.

METHODS: The patients underwent magnetic resonance imaging scans, clinical examination, and QoL assessment by SF-36 questionnaire. Statistics were performed by using Spearman correlation coefficient, Kaplan-Meier plot, Poisson regression model, mixed linear regression models, and mixed logistic regression models.

RESULTS: Mean follow-up time was 55.0 months (26.1 standard deviation, range 10-132). Thirteen patients were lost to follow-up. Serviceable hearing was lost in 54 of 71 (76%) (CM) and 34 of 53 (64%) (GKRS) patients during the study period (not significant, log-rank test). There was a significant reduction in tumor volume over time in the GKRS group. The need for treatment following initial GKRS or CM differed at highly significant levels (log-rank test, $P < .001$). Symptom and QoL development did not differ significantly between the groups.

CONCLUSION: In VS patients, GKRS reduces the tumor growth rate and thereby the incidence rate of new treatment about tenfold. Hearing is lost at similar rates in both groups. Symptoms and QoL seem not to be significantly affected by GKRS.

KEY WORDS: Acoustic neurinoma, Conservative management, Gamma knife radiosurgery, Quality of life, Vestibular schwannoma

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Vestibular schwannomas (VS) are benign tumors with symptoms that cause audiovestibular symptoms and decrease the patient's quality of life (QoL). The symptoms include varying degrees of unilateral hearing loss, tinnitus, vertigo, and imbalance.[1] Treatment options are conservative management (CM), radiosurgery (RS), and microsurgery (MS), although the optimal treatment plan is a subject of controversy. In 2 recent studies based on a large cohort of conservatively managed unilateral VS, we investigated growth rates, long-term development of QoL, and vestibular/auditive symptoms. Furthermore, we analyzed possible association between tumor growth and symptoms.[2,3]

ABBREVIATIONS: CM, conservative management; **CPA,** cerebellopontine angle; **GKRS,** gamma knife radiosurgery; **IAC,** internal acoustic canal; **GR,** Gardner-Robertson; **KM,** Kaplan-Meier; **MS,** microsurgery; **QoL,** quality of life; **RS,** radiosurgery; **SD,** standard deviation; **SF-36,** 36-item short-form health survey; **VAS,** visual analog scale; **VS,** vestibular schwannoma

There are numerous reports analyzing the course of VS patients following RS, but comparisons with patients left untreated are very few, although such studies are mandatory to evaluate the effectiveness of RS. We are aware of 1 study only in which patients harboring intracanalicular VS treated by gamma knife radiosurgery (GKRS) were compared with patients left untreated, and

no such studies investigating tumors extending outside internal acoustic canal (IAC).[4] In this study, we present prospectively collected data of 237 consecutive patients with unilateral VS extending outside IAC and a minimum of 24 months follow-up (mean 55) who initially were allocated either to CM or GKRS.

The primary end points of the study were to measure the effect of GKRS compared with the natural course of the tumor in terms of tumor growth rate and hearing loss. Secondary end points were postinclusion additional treatment, QoL measured by the 36-item short-form health survey (SF-36) and symptom development.

MATERIAL AND METHODS

Patients

During the period 2000 to 2009, 431 patients with an magnetic resonance imaging (MRI) diagnosis of unilateral VS were referred to the Otoneurosurgical group at Haukeland University Hospital and given initial CM (220), GKRS (127), or MS (84). Upon inclusion, patients were advised of management according the following algorithm: cerebellopontine angle (CPA) tumor diameter <20mm: CM, <20 mm and growth: GKRS or MS; 20 to 25 mm: GKRS or MS; >25 mm: MS. In 57 of 127 patients who were allocated to GKRS, the tumor was less than 20 mm at inclusion. Among these patients, 26 had already made a decision that they wanted their tumor treated by GKRS. In 31 cases, we saw the patient after the referring doctor had observed growth. In the remaining 70 patients receiving GKRS, the tumor was more than 20 mm at inclusion (Figure 1). Patients were included if they had unilateral VS extending outside the IAC initially allocated to CM or GKRS and willingness to allow data to be collected for research. Patients with intracanalicular tumors were excluded. The patients underwent regular MRI and clinical follow-up (6 months, 1, 2, and 5 years). Facial and trigeminal function and signs of pyramidal or cerebellar dysfunction were scored. Patient-reported unilateral hearing impairment, tinnitus, vertigo, and unsteadiness were dichotomized (yes/no). Patients responded to a QoL questionnaire (SF-36) and tinnitus and vertigo visual analog scales (VAS) as described by Myrseth et al.[5] Data were registered prospectively and entered into a database. The study protocol was written in 2009 to 2010 during collection of data, and patients eligible for the study were identified through a database search on the criteria above. The study was closed when the final patient had been followed up for 2 years. The Bergen research program on VS has been approved by the National Data Inspectorate (NDS 13199) and the regional ethics committee, and all participants signed a consent form allowing data to be used for study purposes.

Data obtained at baseline and final follow-up were compared group-wise. Student t test and χ^2 test were used.

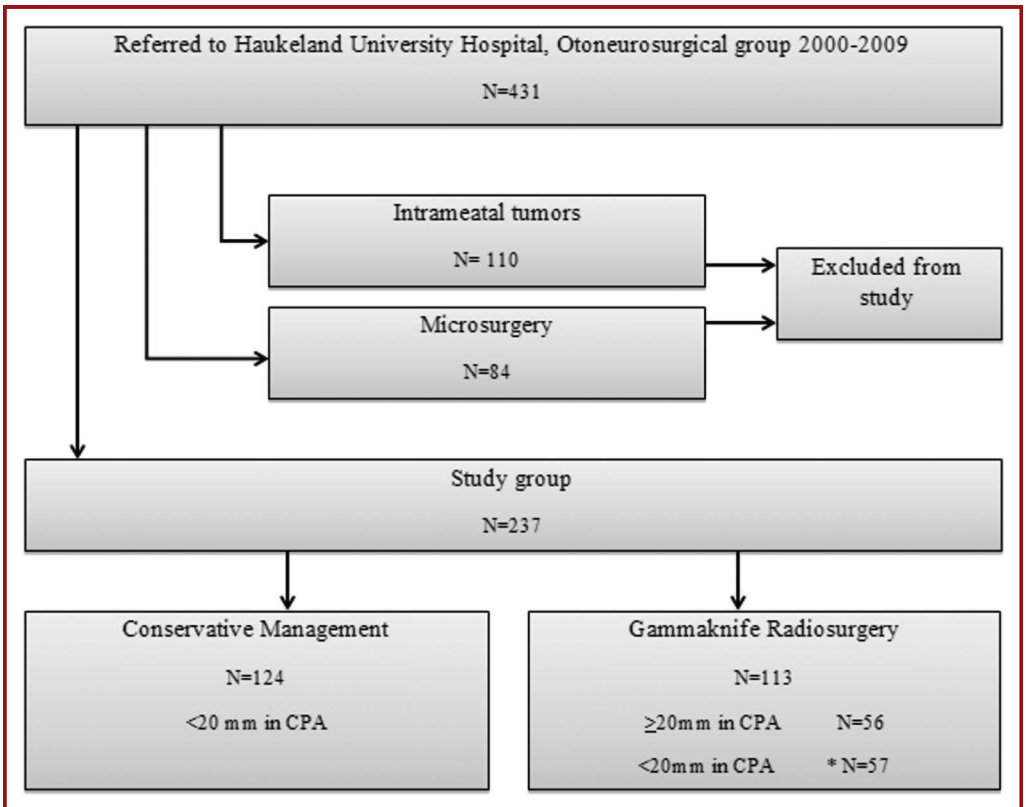

FIGURE 1. *Inclusion criteria. *Altogether 57 patients were treated with GKRS despite smaller size. Of these, 26 patients were referred directly to GKRS upon diagnosis, and 31 patients were observed (CM) outside our hospital and were referred because of growth. GKRS, gamma knife radiosurgery; CM, conservative management.*

The gamma knife treatment was performed by using the Lexel Gamma Knife (Elekta Instruments, Stockholm, Sweden). Both the B and the 4C model (2008) were used. The prescription dose was 12 Gy to the periphery of the tumor with minimum 95% coverage.[6]

Audiometry

More than 95% of audiometry recordings were done at our center. Pure tone audiometry and speech discrimination recordings were used to classify hearing according to the Gardner-Robertson scale (GR).[7] GR1 and GR2 were defined as serviceable. Patients with serviceable hearing at inclusion were compared groupwise. Hearing loss was defined as conversion from "serviceable" to "nonserviceable."

QoL and Symptom Questionnaires

The SF-36 questionnaire was first constructed to survey health status in the Medical Outcomes Study.[8] It comprises 36 items, nonspecific for disease, with 2 to 6 response choices per item. The precoded responses are recoded in percentages. Eight health concepts are created: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, vitality, and general health perceptions. The scores are presented with a minimum of 0 and a maximum of 100. A higher score means a higher health state. Norwegian norm scores are available for reference purposes.[9]

It has been shown that norm data for SF-36 scores are highly age dependant. We therefore constructed representative normative groups for the expected scores using restricted splines for ages below 81, according to the method reported by Hjermstad et al.[10]

Tumor Size

Tumor size measured by the maximum CPA diameter at presentation determined the entry of patients into the CM or GKRS group. It was measured by the largest CPA diameter. For measurement of volume change, tumor volumes were estimated by the slice area method, where the tumor area is traced on each slice, and then used to estimate the tumor volume. The relative tumor volume for each patient was calculated as the ratio between final and initial volume and plotted against observation time. Volume doubling time was calculated by using the volumes of the first and final observation. For tumors that became operated, the final scan before surgery was used.

Statistical Analysis

Statistical analysis was performed by using SPSS 18.0, R gui 2.9.1 and SAS (Statistical Analysis System) version 9.2 (SAS Institute, Inc, Cary, North Carolina) software for Windows. All *P*-values were 2-sided, and values below .05 were considered statistically significant. Missing values of covariates in regression models were treated with the method of listwise deletion, whereas in simple tests the method of pairwise deletion was used.

Continuous variables were reported as means (standard deviation [SD]) and categorical as counts (percent). The difference in proportions of categorical variables was tested by using χ^2, whereas the difference in means was tested using the 2-sample *t* test. Correlation between pairs of variables was estimated using the Spearman correlation coefficient.

Difference in GR change between patients treated with GKRS and those undergoing CM was first analyzed by Kaplan-Meier (KM) survival statistics. Then it was estimated by comparing the incidence rates and ratio of GR change per 100 follow-up months. This was done by using a Poisson regression model with robust variance estimation and the logarithm of time to GR change or study end as offset variable. The above-mentioned procedure was also used to estimate the relative risk difference for the need of a secondary treatment between treated and nontreated at baseline. In all analyses, the intention-to-treat principle was assumed, and tumor size at baseline was considered as a confounding factor.

The difference in SF-36 and VAS between treatment groups (GKRS, CM) was estimated by using mixed linear regression models, whereas the difference in tinnitus, vertigo, and unsteadiness was examined by using mixed logistic regression models. To account for the intraindividual correlation between repeated measures of the same subject, analyses included a random intercept. Inclusion of random slopes had essentially no influence on model fit or results. Because the patients had individual follow-up time and unequal numbers of hospital visits, the analyses of repeated measures were confined to subjects with at least 3 visits within a 60-month period from baseline. In addition, each individual's follow-up time was divided into 5 time intervals using the midpoint categories: 6, 18, 30, 42, and 54 months. Still, the number of visits varied between subjects and may thus have resulted in suboptimal model estimation. All regression analyses included follow-up time (0, 6, 18, 30, 42, and 54 months) and tumor size at baseline as continuous covariates. To test whether SF-36 and VAS and symptoms of the treated and untreated patients changed differently over time, we added a product term of time and treatment (ie, interaction term) to the regression models.

RESULTS

Patients

We identified 237 patients who fulfilled the inclusion criteria, with 113 patients initially given GKRS and 124 patients allocated to CM. Tumor size at inclusion was larger in the treatment group; in all other investigated clinical variables, differences did not reach significant levels. Baseline data for both groups are found in Table 1. Patients were routinely followed up in-hospital by clinical examination and MRI at 1, 2, and 5 years. Additional follow-up was performed as required. The mean follow-up time was 55.0 months (26.1 SD, range 10-132).

TABLE 1. Baseline Data for 113 Patients Receiving GKRS and 124 Patients Managed Conservatively for Vestibular Schwannoma[a]

	GKRS (113)	CM (124)	*P*
Age, mean (SD)	57.7 (13.3)	55.7 (1.1)	NS
Sex (% female)	53.1	53.7	NS
Side (right)	54/113	65/124	NS
Size, cm^3 (SD)	3.9 (3.6)	1.2 (1.2)	.00
Cystic tumor	6	3	NS
Hearing with A/B, n %	48/99 (48.5)	66/116 (54.3)	NS
Tinnitus, n %	80/115 (69.6)	94/122 (77.0)	NS
Vertigo, n %	54/115 (47.0)	58/122 (47.5)	NS
Unsteady, n %	47/115 (40.9)	45/122 (36.9)	NS
Facial numbness	13	3	.02
Facial dysfunction	0	0	NS

[a]GKRS, gamma knife radiosurgery; CM, conservative management; SD, standard deviation, NS, not significant.

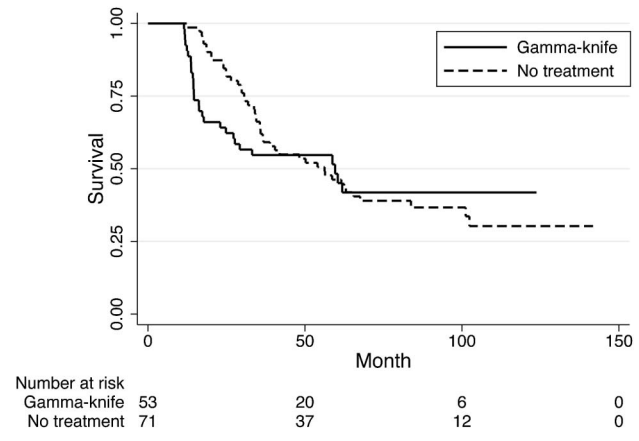

FIGURE 2. *Kaplan-Meier plot of the timewise decline in hearing in 237 patients allocated to initial radiosurgery (GKRS) and CM. GKRS, gamma knife radiosurgery; CM, conservative management.*

The results are based on 918 clinical examinations and 1286 radiological investigations. Thirteen patients were lost to follow-up. Eight patients died before the second control, and the remaining 5 chose follow-up elsewhere. Data were collected by using a standard Case Report Form at each visit and entered into a database. The study was closed when the last patient had been followed up for 2 years.

Missing Data

There were no missing data in symptom registration. In patients with missing baseline audiometry, the first available was used for the KM analysis. There were 864 SF-36 questionnaires. Altogether, 203, 161, and 106 patients filled out 2, 3, and 4 SF-36 questionnaires, respectively.

Hearing

There were 48 (GKRS) and 66 (CM) patients with serviceable hearing at inclusion. The timewise drop in hearing rates defined as conversion from GR A/B into C/D is shown in Figure 2. Ten additional patients were at risk in the KM analysis owing to better registrations at a later time point or missing data at baseline. Statistical analysis revealed a similar decline in hearing rates in both groups (not significant, log-rank test) (Figure 2). Serviceable hearing was lost in 54 of 71 (CM) and 34 of 53 (GKRS) patients during the study period. The incidence rates of hearing loss, as described above, were 1.10 and 1.13 in CM and GKRS groups, respectively (not significant). Tumor size adjusted incidence rate ratio using Poisson regression showed a nonsignificant effect of tumor size on hearing loss (Table 2). Using speech discrimination, we found no significant difference in hearing outcome between the 2 groups, although more patients with initial reduced speech discrimination were found to remain in the 70% to 99% speech discrimination range (Table 3).

Tumor Growth

The relative change in tumor size over time in the 2 groups is shown in Figure 3. There was an overall significant reduction in tumor volume over time in the GKRS group, whereas the tumors in the CM group increased in size (relative volume for CM 1.83 [2.44 SD], for GKRS 0.85 [0.61 SD]). This was reflected in volume doubling time of the 2 groups (3.3 years in CM group vs 14.5 years in GKRS group, indicating tumor shrinkage).

Retreatment

Table 4 shows the number of patients requiring treatment following the initial decision to wait and scan or give GKRS. The incidence rate per 100 months was 0.96 and 0.122 in the GKRS and CM groups, respectively. Using Poisson regression, we found no significant alteration caused by tumor size. Figure 4 shows the proportion of patients in each group who needed treatment throughout the observation period (KM plot). The need for treatment following initial GKRS or CM thus differed at highly significant levels (log-rank test, $P < .001$).

Complications

At the end of the study, 14 (GKRS) and 6 patients (CM) had facial numbness ($P = .08$). One (GKRS) and 6 (CM) patients had facial nerve function worse than grade 3 ($P = .03$) at the end of the study. All facial palsies were seen as a result of surgery following

TABLE 2. Incidence Rate Ratio of First GR Change in Patients With and Without Gamma Treatment[a,b]

						Poisson Regression[c]	
Treatment	No. of Subjects	No. of Subjects With GR Change	Follow-up Time, mo[d]	IR per 100 mo	Tumor Size[e]	Crude IRR (95% CI)	Tumor-size Adjusted IRR (95% CI)
No treatment	71	46	4184	1.10	1.03	1	1
Gamma knife	53	28	2484	1.13	2.95	1.03 (0.62, 1.70)	0.93 (0.48, 1.78)

[a]IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; GR, Gardner-Robertson.
[b]All patients with baseline GR equal to 1 or 2.
[c]Poisson regression model with robust variance estimation. Time to GR change or study end was log-transformed and used as offset.
[d]Sum of months until GR change or study end defined at December 31, 2011.
[e]At baseline.

TABLE 3. Development in Hearing in the CM and GKRS Groups Measured by Speech Discrimination[a,b]

	CM		GKRS			
	Baseline n/n Total	Follow-up (% Baseline)	Baseline n/n Total	Follow-up (% Baseline)	Pearson χ^2	
100% speech discrimination, n (%)	54/120	21 (38.8)	34/100	15 (44.1)	0.579	NS
70%-99% speech discrimination, n (%)	16/120	10 (62.5)	17/100	12 (70.6)	0.863	NS
70 to 100% Speech discrimination	70/120	31 (44.3)	51/100	27 (52.9)	0.158	NS

[a]GKRS, gamma knife radiosurgery; CM, conservative management; NS, not significant.
[b]We found no significant difference between the 2 groups, although more patients with initial reduced speech discrimination were found to remain in the 70% to 99 % speech discrimination range.

failed CM or GKRS, as were the new cases of facial numbness. We did not observe any other complications, such as brainstem dysfunction or radio necrosis.

Tinnitus, Unsteadiness, Vertigo, and QoL

As shown in Figure 5 and Table 5, we observed no statistically significant interaction between time and treatment either before or after adjustment for tumor size at baseline for the reports on tinnitus, unsteadiness, and vertigo. There was a small, but significant decrease in vertigo over time.

As shown in Figure 6 and Table 6, we found a statistically significant interaction between time and treatment for SF-36 role limitations due to personal or emotional problems both before and after adjustment for tumor size at baseline ($P = .017$ and $P = .032$, respectively).

DISCUSSION

GKRS has often been quoted as a safe and effective treatment for small- and medium-sized VS.[1,11-24] Compared with microsurgery, this is well documented.[6,13,15,16,25] However, both safety and effectiveness may be questioned because of the lack of comparison with the natural course in nearly all studies. Several authors, including ourselves, reported slow growth and even good hearing outcomes in a significant proportion of untreated VS cases.[2,3,26-28] To our knowledge, this is the first study to compare the clinical course of extracanalicular VS either treated conservatively or by GKRS.

This study indicates that GKRS, when administered to VS patients, significantly causes growth arrest without interfering negatively with hearing. On the other hand, we did not observe a protective effect of GKRS on hearing, similar to the findings of Regis et al[4] who treated only intracanalicular tumors. As for other complaints and QoL, these appeared to be little affected by treatment.

How Do We Assess the Effect of GKRS?

In scientific studies, the Consensus Meeting on Systems for Reporting Results in Acoustic Neuroma in 2001, reported by Kanzaki et al in 2003, are increasingly used.[29,30] We have adhered to these guidelines in the present study, but chose to include

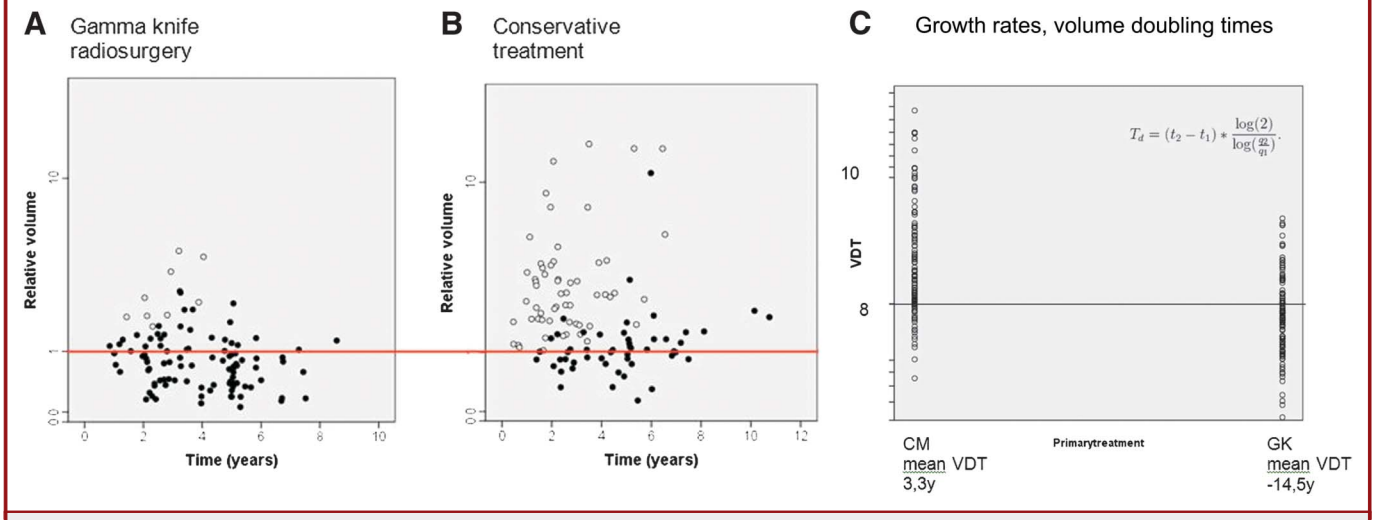

FIGURE 3. *Relative change in tumor volume over time.* **A**, *radiosurgery group.* **B**, *conservatively managed group.* **C**, *growth rate and volume doubling times in both groups. Open circles indicate those patients that were treated with GKRS or MS after the initial allocation to either CM or GKRS group.*

TABLE 4. Incidence Rate and Incidence Rate Ratio of Treatment Following Initial Management Comparing CM and GKRS[a,b]

Baseline Treatment	Re-treatment	Follow-up Time, mo	IR per 100 Months	Tumor Size	Poisson Regression	
					Crude IRR (95% CI)	Tumor-size Adjusted IRR (95% CI)
CM	63/124	7115.5	0.956	1.15	1	1
GKRS	7/113	8227.6	0.122	3.89	0.13 (0.06, 0.25)	0.09 (0.04, 0.21)

[a]IR, incidence rate; IRR, incidence rate ratio; GKRS, gamma knife radiosurgery; CM, conservative management; CI, confidence interval.
[b]Compared with CM, GKRS protects from further treatment with a factor of 1/0.09 (tumor-size adjusted IRR).

volumetric measurements, which has also been done by others, because we feel that growth is better characterized by volumetry than by linear measurements. User-friendly MRI software may in the future allow us to use volumetry instead of linear measurements in the clinical routine without increasing the workload.

The clinical assessment of the effect of GKRS on VS is often based on freedom from re-treatment. This may, however, be heavily biased. In particular, one may be likely to accept volume increase following GKRS as transient enlargement, whereas a similar increase observed in an untreated tumor usually will be interpreted as true growth and thus lead to treatment.[31,32]

Symptom Development and QoL

Recent studies indicate symptoms that are difficult to quantify, such as tinnitus and, in particular, vertigo, may cause more discomfort to the patient than unilateral hearing. In 2006, we showed that vertigo is the symptom interfering the most with QoL measured by SF-36 and Glasgow Benefit Inventory, and this finding has since been confirmed by others.[2,5,33,34] Little is known about the course of VS-related complaints other than reduced hearing following GKRS. The assessment of vertigo/dizziness was done by 2 crude methods, either along a VAS scale or categorically as yes/no. In future studies, tinnitus and vertigo may be assessed by more accurate scales such as the Penn Acoustic Neuroma Quality-of-Life Scale, Dizziness Handicap Inventory, and Tinnitus Handicap Inventory.[35-38] We found a gradual decline in the proportion of patients reporting vertigo, and this drop seemed to be most pronounced in the CM group. One might speculate if vertigo caused by initial unilateral vestibular dysfunction, in many cases, subsides, because vestibular function is lost on the tumor side and compensated by the contralateral vestibular organ.[34] Regarding tinnitus, it is not possible by the measures used in this study to demonstrate any beneficial or negative effect of GKRS on this complaint, which is found in many VS patients. Therefore, it appears that neither vestibular nor auditive symptoms were significantly affected by GKRS. Similarly, the low impact observed after GKRS on the patients' QoL measured by SF-36 confirms that the treatment does not affect patients' perception of disease to any significant degree. It should be noted that SF-36, when administered repeatedly over a long period of time, does reflect any event of some magnitude in an individual's life, and if the impact of symptoms, including their fluctuations are of less magnitude, they are likely to be masked.

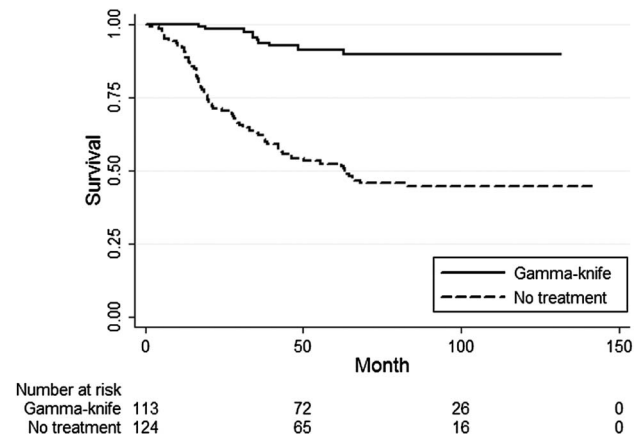

FIGURE 4. *Kaplan-Meier plot showing the need of a secondary treatment following initial radiosurgery or conservative management.*

In general, many studies indicate that VS is to be regarded as an illness causing chronic symptoms that are not necessarily relieved by treating the tumor.[1,2,11,15,18,22] Guidance on how to cope with tinnitus, vertigo, and unilateral hearing loss is probably of equal importance to many patients as having treatment for their tumor. We recently found that vertigo, if a presenting symptom, is associated with a significantly increased risk of dependence on a disability pension within a period of 2 to 5 years (C.N.B., in press).

In this study, we have reported adverse final outcomes as complications, although, for instance, facial palsies may not be directly attributable to GKRS or CM. However, we believe it is important to report the final outcome. It should be noted that the overall occurrence of facial palsies following the treatment algorithm we have chosen is low.

Hearing

We are aware of only 1 study comparing groups of VS patients treated by CM or GKRS.[4] The authors found that, in intracanalicular tumors, hearing preservation rates were similar in both groups, but suggested that GKRS should be offered as "proactive"

TABLE 5. Odds Ratio With 95% Confidence Interval for Symptoms in Generalized Linear Mixed Models With Random Intercept[a]

	Unadjusted		Adjusted for Tumor Size	
Parameters	Time OR (95% CI)	Gamma Knife OR (95% CI)	Time OR (95% CI)	Gamma Knife OR (95% CI)
Tinnitus	1.01 (0.99, 1.02)	0.55 (0.24, 1.23)	1.01 (0.99, 1.02)	0.73 (0.30, 1.92)
Vertigo	0.99 (0.98, 1.00)[b]	0.80 (0.44, 1.44)	0.98 (0.97, 1.00)[c]	1.04 (0.52, 2.01)
Unsteadiness	1.00 (0.99, 1.01)	0.92 (0.48, 1.74)	1.00 (0.99, 1.01)	0.86 (0.40, 1.85)

[a]OR, odds ratio; CI, confidence interval.
[b]$P < .05$.
[c]$P < .01$, indicating a significant interaction between time and treatment.

treatment whatsoever. They also observed growth in a higher proportion of untreated tumors than found in other studies.[3,26] The dose given to tumors with a larger volume is likely to cause cochlear damage in more cases than what was found in the French study. Cochlear dose was not measured routinely in our study and therefore cannot be reported. We did not measure any difference in hearing loss in the 2 groups, and our study therefore suggests that GKRS neither protects or favors hearing loss in extrameatal tumors.

Strengths and Weaknesses of This Study

Although the present study does not hold the full requirements for being prospective, patients were treated by a standardized protocol and all data collection for the database was done prospectively via case report forms and questionnaires. Thus, it is unlikely that the outcome would have differed significantly, given the protocol was written before the start of data collection. One inherent study weakness is the difference in tumor size in the 2 groups. We did not find any other differences than tumor volumes and the occurrence of facial numbness within the baseline clinical characteristics of the 2 groups, and the regression analysis revealed that initial tumor size did not contribute significantly to the various endpoints measured. This is, however, controversial, because other groups have reported strong correlations between size and vestibular symptoms.[34] It is possible that the use of more refined methods, such as disease-specific questionnaires, might reveal differences in symptoms not accounted for here. Further studies will be necessary to elucidate this.

Also, there are several classification systems used to describe hearing acuity. We chose the much-used GR classification, and based on this scale we have chosen to define serviceable hearing as grade 1 and 2. One possible weakness of this system is that it does not include frequencies higher than 2000 Hz. Thus, hearing loss in higher frequencies is not detected by this method.

The division of patients into 2 groups was possible because of our long-time routine of rescanning small tumors instead of giving immediate treatment.

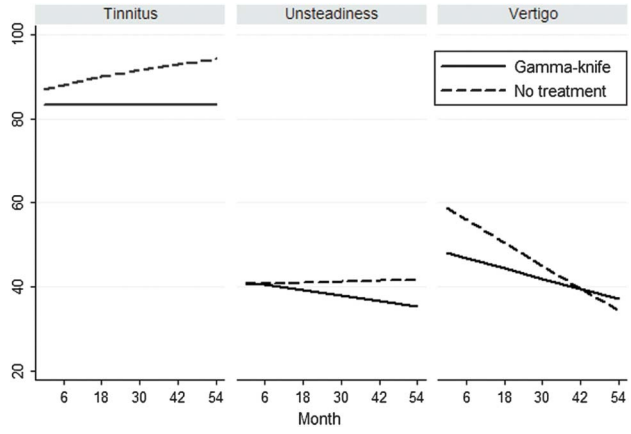

FIGURE 5. *Changes in categorically scored complaints (vertigo, tinnitus, unsteadiness) over time in patients receiving GKRS or CM. Mixed linear regression model estimates (GKRS and CM). GKRS, gamma knife radiosurgery; CM, conservative management.*

Is Wait-and-Scan Feasible?

It has been suggested that RS is so harmless that it may be given to small tumors even if many of them will not grow for many years.[4,22,24,25,39] Our study did not detect any adverse effect from GKRS compared with CM. In order to investigate the best management of small VS (CM or immediate GKRS), it would be optimal to perform prospective randomized studies. If CM is chosen, it is important that the patient adheres to the follow-up program. Furthermore, the doctor assessing the follow-up scans needs access to all scans, earlier and present. It is not sufficient to read the report and assume no change. Both these issues may seem obvious, but, in particular, radiology seems to be violated because patients may undergo scans in different centers each time. The few cases lost in this cohort were followed up elsewhere, and we always examine previous scans together with present. We believe that wait-and-scan may be offered to small tumors, because a large proportion of them will not grow. Repeated comparative studies are needed to show whether

TABLE 6. Estimated Regression Coefficient in Linear Mixed Models With Random Intercept[a]

	Unadjusted		Adjusted for Tumor Size	
Parameters	Time β ± SE	Gamma Knife β ± SE	Time β ± SE	Gamma Knife β ± SE
SF-36pf	0.03 ± 0.03	−1.59 ± 3.27	0.04 ± 0.03	−1.94 ± 3.86
SF-36rp	0.06 ± 0.08	5.33 ± 6.00	0.09 ± 0.08	3.26 ± 7.02
SF-36bp	0.02 ± 0.04	2.04 ± 3.80	0.03 ± 0.04	−1.50 ± 4.46
SF-36gh	0.06 ± 0.04	1.25 ± 3.09	0.09 ± 0.04[b]	0.01 ± 3.62
SF-36vt	0.11 ± 0.04[c]	2.73 ± 3.22	0.12 ± 0.04[c]	0.01 ± 3.77
SF-36sf	−0.05 ± 0.05	1.17 ± 3.26	−0.03 ± 0.05	−0.06 ± 3.83
SF-36re	0.22 ± 0.08[c]	2.97 ± 5.55	0.24 ± 0.08[c]	5.45 ± 6.40
SF-36mh	0.09 ± 0.03[c]	0.92 ± 2.13	0.10 ± 0.03[c]	2.13 ± 2.50
VAS Vertigo	0.01 ± 0.05	−10.0 ± 4.46[b]	0.05 ± 0.05	−4.40 ± 5.22
VAS Tinnitus	0.07 ± 0.06	−10.3 ± 4.41[b]	0.08 ± 0.06	−4.45 ± 5.15

[a]SE, standard error; pf, physical functioning; bp, bodily pain; rp, role limitations due to physical health problems; re, role limitations due to personal or emotional problems; mh, emotional well-being; sf, social functioning; vt, vitality; gh, general health perceptions; VAS, visual analog scale.
[b]$P < .05$.
[c]$P < .01$. A statistically significant interaction between time and treatment was observed for SF-36re both before and after adjustment for tumor size at baseline ($P = .017$ and $P = .032$, respectively).

patients, or groups of patients, benefit from early treatment. If this is proven, today's treatment policy of offering CM to small tumors should be reevaluated. A study from Denmark suggests that conservatively managed patients with normal hearing and small tumors at diagnosis have better hearing outcomes than those with a declining function.[40]

CONCLUSION

In VS patients with extracanalicular tumors, GKRS reduces the tumor growth rate and thereby the incidence rate of new treatment about tenfold. Hearing is lost in treated patients at a similar rate as in untreated. Symptoms and QoL seem not to be

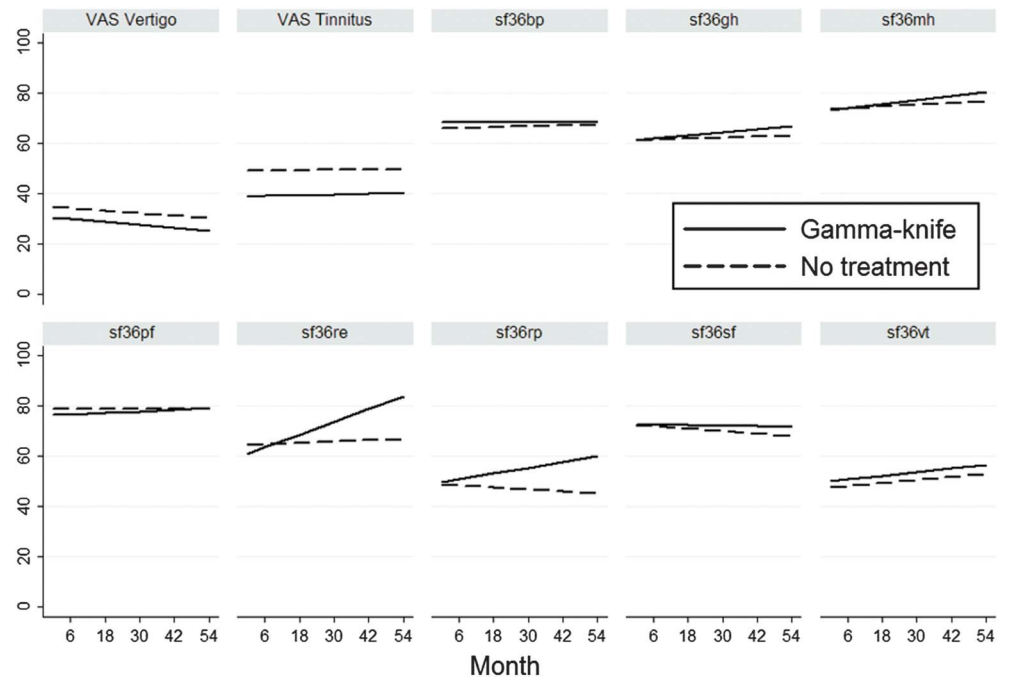

FIGURE 6. *Changes in visual analog scores for vertigo and tinnitus and SF-36 scores over time in the 2 groups of patients (GKRS and CM). Mixed linear regression model estimates. GKRS, gamma knife radiosurgery; CM, conservative management.*

significantly affected by GKRS. No true complications were observed after treatment.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

With increasing availability of MR imaging, the rate of incidentally found vestibular schwannomas (VS) increases. The authors of this study compared the clinical and radiological results in patients with VS after radiosurgery (gamma knife radiosurgery [GKRS]) with a cohort of patients being followed up by a wait-and-scan strategy (conservative management [CM]). Preservation of functional hearing, tumor growth, quality of life, and the necessity to treat/re-treat the patients for their VS were analyzed. Whereas loss of hearing was statistically not different in both cohorts, patients after GKRS showed significantly less tumor growth and, consequently, fewer additional therapeutic interventions. Because

the patients with CM did not have any tumor-specific therapy at the beginning, this finding has to be interpreted as postponement of the treatment—patients initially being just observed received therapy at a later stage, albeit with similar results. The higher incidence of facial palsy in the CM group was attributed to postoperative morbidity and not as a deficit having occurred during the "wait-and-scan" period. The authors have to be congratulated for these data providing important information for patient counseling. This database is even more valuable, because the authors act as a nationwide reference center for VS; thus, they have a very large catchment area with representative data at their disposal. Hence, in cases with small tumors and absence of symptoms, a careful wait-and-scan strategy seems to be reasonable in individual cases as long as the patient is compliant, strictly adhering the audiometric and radiological follow-up. The results of this study add valuable information for the management of patients with VS.

Joerg-Christian Tonn
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Original Amputation Kit Used in the Civil War

The carnage that resulted from frontal attacks, combined with a relatively few number of poorly equipped surgeons led to fairly dismal prospects for any soldier unlucky enough to be shot or otherwise injured in battle. Those with serious injuries in the torso would simply die. For those who were shot in an extremity, the options were few, in fact, really one: amputation.