Gamma Knife radiosurgery for treatment of growing vestibular schwannomas in patients with neurofibromatosis Type 2: a matched cohort study with sporadic vestibular schwannomas

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OBJECTIVE Neurofibromatosis Type 2 (NF2) is a tumor syndrome characterized by an autosomal dominant pattern of inheritance. The hallmark of NF2 is the development of bilateral vestibular schwannomas (VSs), generally by 30 years of age. One of the first-line treatment options for small to medium-large VSs is radiosurgery. Although radiosurgery shows excellent results in sporadic VS, its use in NF2-related VS is still a topic of dispute. The aim of this study was to evaluate long-term tumor control, hearing preservation rates, and factors influencing outcome of optimally dosed, contemporary Gamma Knife radiosurgery (GKRS) for growing VSs in patients with NF2 and compare the findings to data obtained in patients with sporadic VS also treated by means of GKRS.

METHODS The authors performed a retrospective analysis of 47 growing VSs in 34 NF2 patients who underwent GKRS treatment performed with either the Model C or Perfexion Leksell Gamma Knife, with a median margin dose of 11 Gy. Actuarial tumor control rates were estimated using the Kaplan-Meier method. For patient- and treatment-related factors, a Cox proportional hazards model was used to identify predictors of outcome. Trigeminal, facial, and vestibulocochlear nerve function were assessed before and after treatment. NF2-related VS patients were matched 1:1 with sporadic VS patients who were treated in the same institute, and the same indications for treatment, definitions, and dosimetry were used in order to compare outcomes.

RESULTS Actuarial tumor control rates in NF2 patients after 1, 3, 5, and 8 years were 98%, 89%, 87%, and 87%, respectively. Phenotype and tumor volume had significant hazard rates of 0.086 and 22.99, respectively, showing that Feiling-Gardner phenotype and a tumor volume not exceeding 6 cm³ both were associated with significantly better outcome. Actuarial rates of serviceable hearing preservation after 1, 3, 5, and 7 years were 95%, 82%, 59%, and 33%, respectively. None of the patients experienced worsening of trigeminal nerve function. Facial nerve function worsened in 1 patient (2.5%). No significant differences in tumor control, hearing preservation, or complications were found in comparing the results of GKRS for NF2-related VS versus GKRS for sporadic VS.

CONCLUSIONS With modern GKRS, the use of low margin doses for treating growing VSs in patients with NF2 demonstrates good long-term tumor control rates. Feiling-Gardner phenotype and tumor volume smaller than 6 cm³ seem to be independently associated with prolonged progression-free survival, highlighting the clinical importance of phenotype assessment before GKRS treatment. In addition, no significant differences in tumor control rates or complications were found in the matched-control cohort analysis comparing GKRS for VS in patients with NF2 and GKRS for sporadic VS. These results show that GKRS is a valid treatment option for NF2-related VS, in addition to being a good option for sporadic VS, particularly in patients with the Feiling-Gardner phenotype and/or tumors that are small to medium in size. Larger tumors in patients with the Wishart phenotype appear to respond poorly to radiosurgery, and other treatment modalities should therefore be considered in such cases.

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KEY WORDS neurofibromatosis Type 2; Gamma Knife radiosurgery; vestibular schwannoma; tumor control; hearing preservation; skull base
NEUROFIIBROMATOSIS Type 2 (NF2) is an inherited syndrome characterized by the presence of multiple benign tumors of the nervous system. The syndrome is inherited in an autosomal dominant pattern and is caused by mutations in the NF2 tumor suppressor gene, which encodes for the protein merlin and is located on the long arm of chromosome 22. NF2 is generally classified into 2 phenotypes. The Wishart phenotype is characterized by rapidly progressing multiple cerebral and spinal lesions in patients younger than 20 years, whereas the Feiling-Gardner phenotype is characterized by slowly progressing central tumors first identified when the patient is older than 20 years. The hallmark of NF2 is bilateral vestibular schwannomas (VSs), generally developing by 30 years of age. These tumors cause tinnitus, balance dysfunction, and hearing loss, eventually leading to complete deafness. If left untreated, VSs can extend medially and cause brainstem compression and hydrocephalus. One of the first-line treatment options for small to medium-large VSs is radiosurgery. The advantage of radiosurgery compared with microsurgery, apart from its being less invasive, is the higher rate of serviceable hearing retained after treatment. Current available studies on Gamma Knife radiosurgery (GKRS) for sporadic VS are abundant and show excellent results for tumor control and adverse effects. For NF2-related VS, the number of studies is limited, and the studies show varying tumor control rates. Consequently, the use of radiosurgery as a first-line treatment option is controversial. No comparison in tumor control rates between GKRS for NF2-related VS and sporadic VS has previously been made in a matched cohort study. In addition, all currently available publications, except one small case series with short follow-up, present treatment results of the period before implementation of the new-generation Leksell Gamma Knife with automatic positioning system (Model C and Perfexion). In this study, we evaluated long-term tumor control, side effects, and factors influencing the outcome of optimally dosed modern GKRS for VS in a relatively large cohort of NF2 patients. In addition, this is the first study to use matched cohort analysis to compare the results of GKRS treatment in patients with NF2 to results in patients with sporadic (non-NF2) VS.

Methods

Study Population

We performed a retrospective cohort analysis by reviewing a large prospectively maintained database of all cases of VS treated with the Gamma Knife in the Gamma Knife Center Tilburg between 2002 and 2014. This study population was formed after applying the following exclusion criteria: previous GKRS or other radiosurgery on VS and/or not clearly fulfilling the Manchester criteria. A total of 34 patients with 47 VSs qualified for inclusion in the study; 13 patients were treated on both sides and in those cases the 2 treatments were both included in the analysis as separate cases. The initial management strategy after diagnosis of NF2 whenever feasible was wait-and-scan. GKRS was performed for small to medium-large tumors showing radiological progression, with or without progressive hearing loss. For tumors with a large volume at initial presentation, a wait-and-scan policy was not considered appropriate and treatment was advised. There is not a well-defined volumetric cut-off for the decision to treat larger tumors with radiosurgery or microsurgery. Generally patients with tumors with a volume below 10 cm³ are accepted for radiosurgery, unless symptoms of mass effect are present. For treatment of tumors larger than 10 cm³, microsurgery alone or debulking followed by GKRS is advised. However, in some cases, such large tumors may be treated with radiosurgery when microsurgery is contraindicated due to comorbidity, high age, or if the only remaining serviceable hearing is on the side to be treated. The decision to treat with GKRS was made by the radiosurgical team, consisting of a radiation oncologist and neurosurgeons. A summary of patient, tumor, and treatment characteristics is presented in Table 1.

GKRS Procedure

For all patients, T1-weighted MRI with and without gadolinium enhancement, as well as T2-weighted MRI, were performed for dose planning. The slice thickness was usually 1 or 2 mm, without a slice gap. Until November 2008, a total of 29 tumors were treated with the Leksell Gamma Knife 4C Model (Elekta AB). Thereafter, 18 tumors were treated with the Leksell Gamma Knife Perfexion (Elekta AB). A Leksell Model G head frame (Elekta AB, Stockholm, Sweden) was placed under local anesthesia. Planning was done with Leksell GammaPlan software (Elekta AB). Dosimetric analysis included iso-dose, coverage, prescription dose, and margin and maximum radiation doses to tumors in all patients and margin and maximum radiation dose to the cochlea in patients with serviceable hearing prior to GKRS.

Tumor characteristics, including empty fundus, cystic component, and tumor volume, were assessed with MRI (Table 1).

Follow-Up Evaluations

Clinical evaluation was performed 3 months after GKRS, followed by annual clinical and radiological evaluations if the patient’s condition was stable. Follow-up intervals were shortened in the event of hearing deterioration or radiographic evidence of progression. Audiograms, if available, were obtained from the referring hospitals until the patient had lost serviceable hearing.

Loss of tumor control was defined as the need for additional treatment (GKRS or microsurgery) because of confirmed growth on 2 consecutive MRI studies or worsening of symptoms (i.e., brainstem compression) making acute intervention necessary. There is no uniform definition of progression, but we generally adhered to a minimum diameter increase of 2 mm in any direction. Tumor expansions due to transient radiation-induced swelling were taken into account and ruled out as progression by evaluation on consecutive MRI studies, although new insights regarding transient swelling after GKRS treatment led to a more expectant attitude in the second half of the study period compared with the first half. The final decision as to whether a tumor required additional treatment was made.
in a multidisciplinary session involving at least a neurosurgeon, a radiation oncologist, and a radiologist.

Audiometry before and after treatment was used to assess hearing preservation rates, defined as serviceable hearing (Gardner-Robertson Hearing Scale, Grade I and II) after treatment.

Complications defined as facial neuropathy, according to the House-Brackmann grading system, and trigeminal neuropathy (i.e., numbness, paresthesia, or neuralgia) were assessed at baseline and during follow-up. Complications with a duration of less than 1 year were defined as transient whereas those with a duration of more than 1 year were defined as permanent. In case of missing data or loss of patients to follow-up, we contacted other hospitals in an attempt to collect the missing data.

Match Control Analyses

To compare time to loss of tumor control in NF2 versus non-NF2 cases (sporadic VS), we matched our cohort 1:1 with patients who underwent GKRS for sporadic VS in our institute. The treatment protocol was similar for both groups in terms of indication for treatment (only growing or large VS), GKRS parameters, definitions of tumor response and failure, and follow-up evaluation. The following matching scheme was used:

1. Age at GKRS ± 1 year. If this age matching is not possible, patients are matched on tumor volume first. Second, the age of the control closest to the patient is chosen, but with the control’s age always higher than that of the NF2 patient, because older age is associated with a better outcome in NF2 patients. This will add power to the conclusion if no difference is found.
2. Tumor volume ± 0.5 cm³. If this volume matching is not possible, a control with the nearest, although always smaller, tumor volume is used, because smaller tumor volume is associated with better outcome as shown in sporadic VS. This will add power to the conclusion if no difference is found.
3. If possible, the period of treatment is matched (before vs after 2008), because of implementation of the Gamma Knife Perfexion and in order to avoid large differences in follow-up length.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at GKRS in yrs (range)</td>
<td>40 (13–71)</td>
</tr>
<tr>
<td>Sex*</td>
<td>Female 26 (55%) Male 21 (45%)</td>
</tr>
<tr>
<td>Side</td>
<td>Left 24 (51%) Right 23 (49%)</td>
</tr>
<tr>
<td>Koos grade</td>
<td>1 10 (21%) 2 14 (30%) 3 10 (21%) 4 13 (28%)</td>
</tr>
<tr>
<td>Fundus empty</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Wishart 13 (28%) Feiling-Gardner 34 (72%)</td>
</tr>
<tr>
<td>Tumors other than VSs at time of GKRS</td>
<td>None 16 (34%) Cranial tumor(s) 11 (23%) Non-cranial tumor(s) 5 (11%) Cranial &amp; non-cranial tumors 15 (32%)</td>
</tr>
<tr>
<td>GKRS Primary treatment</td>
<td>31 (66%)</td>
</tr>
<tr>
<td>Combination of debulking followed by GKRS</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Secondary treatment (initially microsurgery)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Pre-GKRS GR grade</td>
<td>I 14 (30%) II 9 (19%) III 2 (4%) IV 1 (2%) V 18 (38%) Not documented 4 (9%)</td>
</tr>
<tr>
<td>Indication</td>
<td>Tumor growth 41 (87%) Tumor volume 3 (6%) Not documented 3 (6%)</td>
</tr>
<tr>
<td>TGI</td>
<td>Not documented</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Trigeminal neuropathy 4 (10%)‡ Tinnitus 22 (54%)‡ Vertigo 17 (36%)§</td>
</tr>
<tr>
<td>Facial neuropathy (HB class)</td>
<td>I 28 (60%) II 2 (4%) III 1 (2%) IV 2 (4%) V 5 (11%) VI 3 (6%) Not documented 6 (13%)</td>
</tr>
<tr>
<td>VS vol in cm³, median (range)</td>
<td>3.1 (0.1–14.4)</td>
</tr>
<tr>
<td>Prescription dose in Gy, median (range)</td>
<td>13 (11–13)</td>
</tr>
<tr>
<td>Isodose, median (range)</td>
<td>60% (44–71%)</td>
</tr>
<tr>
<td>Coverage, median (range)</td>
<td>90% (90–100%)</td>
</tr>
</tbody>
</table>

* Patient sex is given here for each tumor.
‡ For 5 tumors the presence or absence of trigeminal neuropathy was not documented.
§ For 6 tumors the presence or absence of tinnitus was not documented.

HB = House-Brackmann; GR = Gardner-Robertson.

Values are numbers of tumors (%) unless otherwise indicated. The cohort included 34 patients with 47 tumors (47 treated sides).
Statistical Analyses

Survival analysis was performed for time to loss of tumor control and time to nonserviceable hearing using the Kaplan-Meier method. Differences between strata were tested for significance using the log-rank test. To assess the impact of factors of interest on progression-free survival (PFS), univariate and multivariate associations were evaluated using a Cox proportional hazards regression model. Patient factors (age at the time of radiosurgery, phenotype, tumor volume, and macrocytic features) and treatment-related factors (marginal dose tumor, maximum dose tumor, cochlear dose, and microsurgical debulking) were included in the analysis. For the matched-control analysis, differences in tumor control rates were assessed using the Kaplan-Meier method. Differences in complication rates were assessed with the Fisher exact test. All tests were performed with SPSS version 20 (IBM Corp.).

Results

Tumor Control and Factors Associated With PFS in NF2 patients

The median duration of radiological follow-up was 70 months (mean 63 months, range 7–143 months). During this period 3 patients (with 3 [6%] of the 47 treated tumors, mean age 70 years) died. Only 1 patient died due to progression of NF2. In this patient loss of tumor control occurred, making new intervention (surgery) necessary. Nonetheless, the patient died due to complications of NF2 less than 3 years after this new intervention. The most recent MRI follow-up showed that of the 47 VSs that were treated with GKRS, 18 tumors (38%) decreased in size, 23 tumors (49%) were stable (defined as no increase in any diameter of more than 2 mm on consecutive MRI scans, compared with initial tumor diameter), and 6 tumors (13%) showed tumor progression requiring additional intervention. Of the tumors that showed progression, 4 were treated with microsurgery and 2 were treated with GKRS as a new intervention. The median time to loss of tumor control was 24 months (range 9–37 months). Actuarial tumor control rates after 1, 3, 5, and 8 years were 98%, 89%, 87%, and 87%, respectively (Fig. 1).

In univariate analysis (using the log-rank statistic in Kaplan-Meier plots), the following p values for association with longer PFS were found: p = 0.003 for tumor volume \( \leq 6 \text{ cm}^3 \) (Fig. 2), p = 0.065 for noncystic tumor, p = 0.30 for microsurgical debulking, and p = 0.022 for Feiling-Gardner phenotype (Fig. 3). For continuous variables, univariate Cox regression analysis was performed. Smaller tumor volume (p = 0.012) was found to be a significant predictor for tumor control. Increasing age (p = 0.204), margin dose (p = 0.244), and maximum dose (p = 0.783) were not significant. To assess whether significant univariate factors were independently significant, a multivariate Cox regression analysis was performed. Because of the limited number of events, not all variables could be added in the analysis, therefore the results of multivariable Cox regression should be interpreted with caution. Nevertheless, it seems that phenotype and tumor volume are independent factors associated with PFS (Table 2). We therefore plotted another Kaplan-Meier curve wherein each phenotype was stratified with respect to tumor volume (\( \leq 6 \text{ cm}^3 \) vs > 6 cm³) (Fig. 4), showing excellent tumor control rates for both Feiling-Gardner phenotype groups as well as Wishart phenotype with tumor volumes \( \leq 6 \text{ cm}^3 \), but also demonstrating the impact that the combination Wishart phenotype and tumor volume > 6 cm³ has on tumor control rates (Table 3).
Tumor Control in NF2 Versus Non-NF2 Patients Treated With GKRS for a Growing VS

The median difference in age at GKRS between the NF2 and non-NF2 groups was 1.00 year (SD 3.87 years, range 0–16 years) and the difference in tumor volume was 0.27 cm$^3$ (SD 0.54 cm$^3$, range 0–2.90 cm$^3$). In the non-NF2 group, 4 patients had loss of tumor control; the median time to loss of tumor control and therefore the need of a new intervention in this group was 36 months (range 25–60 months). In the non-NF2 group, the actuarial tumor control rates after 1, 3, 5, and 8 years were, respectively, 100%, 94%, 91%, and 91%. We compared the actuarial tu-
mor control rates in NF2 versus non-NF2 patients by use of the log-rank statistic in Kaplan-Meier plots, which resulted in a chi-square of 0.772 with \( p = 0.379 \). Therefore, there was no significant difference in tumor control rates after GKRS for NF2-related VS and sporadic VS in these cohorts (Fig. 5).

Hearing Preservation in NF2 patients

The median duration of audiological follow-up was 40 months (mean 40 months, range 1–102 months). Before GKRS, 23 ears had serviceable hearing (Gardner-Robertson Grade I or II). One patient was lost to follow-up. The latest audiological follow-up examinations showed that of the 22 sides treated with GKRS, 10 (46%) had stable hearing; hearing worsened but remained serviceable in 4 sides (18%), and in 8 (36%) sides, serviceable hearing was lost. The total serviceable hearing preservation rate was 64%, defined as Class I or II. Actuarial preservation rates of serviceable hearing after 1, 3, 5, and 7 years were 95%, 82%, 59%, and 33%, respectively (Fig. 6). It is important to note that all but one of the patients with serviceable hearing had audiological follow-up of more than 12 months. Four patients lost serviceable hearing within 7 months after treatment. Due to the small group size, no further statistical analysis for factors influencing outcome was performed.

Complications

In the NF2 group, 4 of 41 tumors produced symptoms of trigeminal neuropathy before GKRS. After GKRS no patient suffered worsening of or new symptoms of trigeminal neuropathy, and 1 patient experienced improvement. Of the 40 treated sides with complete facial nerve data, only 2 (5%) had a post-GKRS worsening in House-Brackmann grade (Grade I to II and Grade I to IV, respectively), and the worsening was permanent only in the latter case (for a rate of 2.5%). In the non-NF2 group only 1 patient had post-GKRS permanent worsening in House-Brackmann grade, and 1 patient had worsening of trigeminal neuropathy symptoms. Therefore, in the matched-control cohort analysis for complications using the Fisher exact test, no significant differences in permanent increase of facial neuropathy (\( p = 1.0 \)) or trigeminal neuropathy (\( p = 1.0 \)) were found. These results suggest that NF2 mutations do not seem to give significant additional risk for facial or trigeminal nerve complications due to GKRS.

Discussion

Tumor Control After GKRS in NF2

The main goal of GKRS is tumor control through arrest of tumor growth, whereas in surgical treatment the main goal is elimination of the tumor itself. In this study we show that the rate of tumor control for growing VSs in patients with NF2 treated with GKRS was 87% at 5

![FIG. 4. Kaplan-Meier plot illustrating tumor control in 47 NF2-related VSs stratified by phenotype and tumor volume as follows: Felling-Gardner and tumor volume ≤ 6 cm³ (indicated by A), Wishart and tumor volume ≤ 6 cm³ (indicated by B), Felling-Gardner and tumor volume > 6 cm³ (indicated by C), and Wishart and tumor volume > 6 cm³ (indicated by D).](image-url)
years. In 2 of the 6 NF2 patients with a loss of tumor control, this was observed within 1 year after GKRS. During the study period new insights have led to a more conservative attitude toward tumor expansion within the first 2 years after GKRS due to transient swelling. Therefore, treatment might not have been considered to have failed in some cases according to the current definition of tumor control, which takes the phenomenon of transient swelling into account. In Table 4 we compare our results with those reported in previous studies. Due to the large difference in median length of follow-up, comparison between studies should be based on actuarial tumor control rates. The highest 5-year tumor control rate was 87%; this is the rate reported by Sun and Liu as well as being the rate that we achieved in this present study. In older studies, the actuarial 5-year tumor control rates are much lower. Our median margin dose is the lowest of all studies in the comparison (11 Gy compared with 12 Gy or higher). Mallory et al. and Phi et al. found that higher margin dosing led to more tumor regression, although with comparable overall tumor control rates and relatively poor hearing outcome. As our data suggest, it appears that comparable, high long-term local tumor control with fewer complications can be achieved with modern GKRS using a lower margin dose, although the factors discussed below could account for overall differences found.

In the multivariate analysis, Wishart phenotype and tumor volumes exceeding 6 cm\(^3\) were independently associated with shortened PFS. This association between phenotype and tumor control was also found by Sun and Liu. In fact, Mathieu et al. and Phi et al. found younger patient age, associated with phenotype, to be associated with shortened PFS. It is known that different NF2 mutations result in either loss of/reduced protein function (large deletions) or gain of protein function (nonsense and frameshift mutations). The gain-of-protein-function mutations are associated with a lower age of onset of disease and more severe symptoms. The difference between mutation types

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Wishart &amp; ≤6 cm(^3)</th>
<th>Wishart &amp; &gt;6 cm(^3)</th>
<th>FG &amp; ≤6 cm(^3)</th>
<th>FG &amp; &gt;6 cm(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wishart &amp; ≤6 cm(^3)</td>
<td>(\chi^2) 3.515</td>
<td>(p) 0.061</td>
<td>(\chi^2) 2.625</td>
<td>(p) 0.105</td>
</tr>
<tr>
<td>Wishart &amp; &gt;6 cm(^3)</td>
<td>(\chi^2) 3.515</td>
<td>(p) 0.061</td>
<td>(\chi^2) 18.738</td>
<td>(p) 0.000</td>
</tr>
<tr>
<td>FG &amp; ≤6 cm(^3)</td>
<td>(\chi^2) 2.625</td>
<td>(p) 0.105</td>
<td>(\chi^2) 4.054</td>
<td>(p) 0.044</td>
</tr>
<tr>
<td>FG &amp; &gt;6 cm(^3)</td>
<td>(\chi^2) 0.089</td>
<td>(p) 0.766</td>
<td>(\chi^2) 4.660</td>
<td>(p) 0.031</td>
</tr>
</tbody>
</table>

FG = Feiling-Gardner.
and therefore the proportion of both phenotypes might explain the difference in outcome of GKRS reported in the various published series.

The view that a larger tumor volume is an independent factor associated with shortened PFS is supported by multivariate analysis done by Klijn et al. in sporadic VS. Their findings, as well as those of the present study, show that GKRS has a significant better tumor control rate for small to medium-sized tumors (≤ 6 cm³) than for large tumors (> 6 cm³).

Other factors that might influence overall tumor control rates are differences in definition of tumor control itself, as was found in comparing previous series, and the proportion of patients who underwent debulking surgery before GKRS, which could delay or eliminate the need for retreatment even for slowly enlarging tumors, as well as the indications for treating these tumors. Centers treating only tumors with evidence of radiological progression may be expected to have less favorable outcomes than centers that treat stable tumors as well. Indications for GKRS have changed over time, reflecting evolving treatment paradigms. In older studies, hearing deterioration without tumor growth was an indication for treatment as well. Now, treatment is only undertaken in case of confirmed growth or tumor volumes at presentation that necessitate intervention. In this series, 88% of the tumors showed growth at the time of treatment; in 6% the indication was not stated (although all were small); and 6% were treated immediately after diagnosis because of large tumor volume, and therefore growth could not be determined. To accurately compare results, studies need to specify their indications for GKRS and the distribution of these indications. In many available studies these indications are not specified.

Comparison of Tumor Control Rates in NF2-Related and Sporadic VS

The use of GKRS in sporadic VS is well established, while the use in NF2 is still a matter of dispute. To address this controversy, we performed a matched-control cohort analysis in tumor control rates after GKRS for NF2-related VS versus sporadic VS, both treated in the same institute, making this study the first to do so. The large group of cases of treated sporadic VS in our institute made accurate matching possible. This approach eliminates the influence on tumor control rates of possible confounders such as age, tumor size, or treatment indication (growing vs stable tumors). Moreover, dosimetry and definitions of treatment failure were applied similarly in both groups. We have shown that tumor control rates did not differ significantly between NF2-related and sporadic VS. Therefore, GKRS is, in our view, a valid choice for the treatment of VS, regardless of the underlying cause of the tumor.

Facial and Trigeminal Nerve Dysfunction

The use of lower marginal dosages used in modern GKRS may explain the low complication rates in recent studies compared with older ones. The low complication rates with respect to facial neuropathy (2.5%) and trigeminal neuropathy (0%) in our study are also seen in the study by Massager et al., in which all patients were also treated with more advanced Gamma Knife models with improved conformity and selectivity and no adverse events were reported. This is in contrast with the recent study by Mallory et al., who reported that facial weakness occurred after GKRS of NF2-related VS in 50% of patients who had normal function before treatment. They attribute this finding to the higher doses and less sophisticated treatment plan-
Radiosurgery for NF2-related and sporadic VS

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93% and a 15-year rate of 17%. Sun and Liu 36 did not able hearing after GKRS varies. However, Timmer et al. 37

serviceable hearing. Apparently, preservation of service - find factors associated with higher preservation rates of

Hearing Preservation

One of the advantages of radiosurgery compared with microsurgery is the higher rate of preservation of serviceable hearing. 15 This preservation rate of serviceable hearing in NF2 patients after GKRS varies between 25% and 78%. 17,18,20,24,30,33,36 One problem encountered in almost all studies is the limited number of NF2 patients with serviceable hearing before treatment and therefore available for audiological follow-up. Our actuarial 5-year rate of hearing preservation is 59%. Mathieu et al. 20 reported a 5-year rate of 48%, and Sun and Liu 36 reported a 5-year rate of 93% and a 15-year rate of 17%. Sun and Liu 36 did not find factors associated with higher preservation rates of serviceable hearing. Apparently, preservation of serviceable hearing after GKRS varies. However, Timmer et al. 17 showed that in patients treated for sporadic VS there is a negative correlation between maximum cochlear dose and hearing preservation. We now aim to keep the cochlear dose below 4 Gy, when possible, assuming that this may lead to better rates of preservation of serviceable hearing. Nonetheless, mechanisms other than direct radiation of

the cochlea might play an important role in hearing loss after GKRS as well. The mechanisms by which the VS itself causes hearing loss are not understood. Tumor growth and tumor size do not seem to correlate with the degree and progression of hearing loss. 1,9,11,19 Some patients show

progressive hearing loss with nongrowing VS, while oth - ers have growing VS without any hearing loss. In addi - tion, hearing loss can be gradual, stepwise, relapsing and remitting, or sudden. These variable patterns of hearing

loss suggest that additional mechanisms play a crucial
depth. 3- and 5-year hearing preservation rates of 82% and 58%

no valid matched-control cohort analysis could be done for hearing preservation. An analysis of the entire cohort of sporadic VSs treated in our institution during the same period with a similar treatment protocol showed overall actuarial 3-year and 5-year hearing preservation rates of 65% and 42%, respectively. 14 Compared with the actuarial 3- and 5-year hearing preservation rates of 82% and 58%
found in NF2 patients, outcome for NF2-related VS do not seem to differ significantly. These results suggest that NF2 mutations do not seem to give additional risk for loss of useful hearing due to GKRS.

Malignant Transformation

Assessing malignant transformation in VS after GKRS is difficult. To be considered a radiation-induced malignancy, a tumor must fulfill Cahan’s criteria. The problem in fulfilling these criteria with respect to VS is that pretreatment biopsies are rarely obtained. Therefore, it is unknown at the time of GKRS whether the tumor is benign or malignant. A recent review of the literature on malignant transformation in VS by Seferis et al. showed that a total of 11 NF2-related VSs underwent secondary malignant transformation after radiosurgery after a median interval of 60 months. Histological examination proved that the tumor was benign before radiation treatment, therefore fulfilling Cahan’s criteria, in only 1 case. Malignant transformation prior to GKRS, as has been observed in 5 NF2 patients, was possible in the other cases. Seferis et al. reported that the risk of malignancy in VS (both sporadic and NF2-related) during a 20-year period in which no radiation was used was 1.32–2.08 per 100,000. The analysis of published cases reveals that after radiation treatment the overall risk over 20 years is 25.1 per 100,000. The use of radiation treatment increases the risk by approximately 15 times in NF and non-NF cases combined. For NF2 cases, the increase in risk is expected to be even greater, although exact numbers are lacking. Baser et al. estimated a risk of 4717 per 100,000 based on a population of 1348 patients with NF2. Rowe et al. estimated the risk to be 1%. Although malignant transformation was not encountered in any of the studies assessed in our comparison (454 treated NF-2 related VSs), available information clearly indicates that there is a real chance of malignant transformation due to GKRS in NF2, but the estimated risk seems very low. The alternative treatment option for VS is microsurgery. It is estimated that the mortality rate after craniotomy for VS removal is around 1%. The possibility of inducing malignant transformation by GKRS should therefore not be used as an argument to choose microsurgery over GKRS.

Study Limitations (and Future Directions)

Because of the long time span of this study, indications for treatment and criteria to define failure of tumor control may have changed over the course of the study period. New insights have led to a more conservative attitude regarding new intervention within 1–2 years after initial GKRS, because of transient swelling. The retrospective study design is a limitation. We were dependent on the availability and accuracy of data in our (prospectively maintained) departmental database and the medical records. We are aware of the inherent risk of selection bias in retrospective studies. However, in this particular study this risk is mitigated by the fact that all tumors that met the indications for treatment were treated by GKRS. No selection was made in advance for other treatments.

Because of the small sample size, and especially the small number of event outcomes, of the multivariate analysis, the results must be interpreted with caution. Assessment of symptoms that are more difficult to objectify (i.e., tinnitus and vertigo) cannot be accurately evaluated based on chart review. Since this work was done, we have implemented validated tinnitus and vertigo scores for the purpose of future research.

Assessment of preservation rates of serviceable hearing should be interpreted with caution. First, as stated before, mechanisms of hearing loss in NF2 are not understood, and they are not necessarily associated with radiosurgical treatment itself. Second, audiological follow-up was incomplete in our study. Our center is a tertiary referral center, and follow-up audiograms are performed at the referring centers, not at our center. Criteria for audiometry might differ among these centers. Most centers perform audiology only if the patient experiences worsening of hearing. Therefore, results may have been biased, and may lead to an underestimation of preservation rates of serviceable hearing.

Future studies are needed to assess mechanisms of hearing loss due to VS to understand and interpret hearing preservation rates after GKRS. In addition, phenotype distribution, indication for treatment, and uniform definitions regarding tumor response must be stated in order to facilitate accurate comparison between studies.

Conclusions

With modern GKRS, the use of low margin doses for treating growing VSs in patients with NF2 shows good long-term tumor control rates. Feiling-Gardner phenotype and tumor volume smaller than 6 cm³ seem to be independently associated with prolonged PFS, highlighting the clinical importance of phenotype assessment before treatment. In addition, no significant differences in tumor control rates and complications were found in our matched-control cohort analysis comparing GKRS in NF2-related VS and sporadic VSs. These results show that GKRS is a valid treatment option for NF2-related VS, in addition to being a good option for sporadic VS, particularly in patients with Feiling-Gardner phenotype and/or small- to medium-sized tumors. Larger tumors in the Wishart phenotype appear to respond poorly to radiosurgery, and other treatment modalities should therefore be considered.

References

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