A schwannoma is a tumor that arises from Schwann cells of the nerve sheath. It is also called a neurilemmoma, neuroma, and neurinoma. Schwannomas most frequently affect CN VIII. Stereotactic radiosurgery has played a significant role as of late in the management of patients with vestibular schwannomas.3,7,11,16,24,26,30

The term “nonacoustic neuroma” or “nonvestibular schwannoma” was used in the medical literature in 1982, when Nedzelski and Tator,25 in Toronto, reviewed 8 cases involving patients with nonacoustic neuromas undergoing surgical resections between 1976 and 1981. Since then, many publications regarding this group of tumors have been added to the literature.5,13,31,35,40 Nonvestibular schwannomas are much more rare and represent less than 0.5% of all intracranial neoplasms.29 Of these, trigeminal schwannomas are the most common ones, accounting for 0.8%–8% of all intracranial schwannomas and 0.1%–0.5% of intracranial tumors.17,22,27,33,35,38,43 Nonvestibular schwannomas in patients with neurofibromatosis most commonly arise from the oculomotor and trigeminal nerves.3 Patients present with differing symptoms related to the nerve from which the schwannoma arises.

Historically, microsurgical resection of intracranial schwannomas has been the standard treatment. Complete resection can, of course, be curative for such lesions, but it is not always feasible, particularly if neurological function of the affected nerve is high at presentation, and preservation of function is desired. Moreover, resection can be associated with unintended neurological deficits and other rare but potentially serious complications.27,35 Radiosurgery offers a minimally invasive alternative to microsurgery for treatment of nonvestibular schwannomas. In this study, we examine our experience treating Gamma Knife surgery for nonvestibular schwannomas:

Clinical article

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Object. Most intracranial schwannomas arise from cranial nerve (CN) VIII. Stereotactic radiosurgery is a mainstay of treatment for vestibular schwannomas. Intracranial schwannomas arising from other CNs are much less common. We evaluate the efficacy of Gamma Knife surgery on nonvestibular schwannomas including trigeminal, hypoglossal, abducent, facial, troclear, oculomotor, glossopharyngeal, and jugular foramen tumors.

Methods. Thirty-six patients with nonvestibular schwannomas were treated at the University of Virginia Gamma Knife center from 1989 to 2008. The median patient age was 48 years (mean 45.6 years, range 10–72 years). Schwannomas arose from the following CNs: CN III (in 1 patient), CN IV (in 1), CN V (in 25), CN VI (in 2), CN VII (in 1), CN IX (in 1), and CN XII (in 3). In 2 patients, tumors arose from the jugular foramen. The median tumor volume was 2.9 cm³ (mean 3.5 cm³, range 0.07–8.8 cm³). The median margin dose was 13.5 Gy (range 9.3–20 Gy); the median maximum dose was 30 Gy (range 21.7–50.0 Gy).

Results. The mean and median follow-up times of 36 patients were 54 and 37 months, respectively (range 2–180 months). At the last radiological follow-up, the tumor size had decreased in 20 patients, remained stable in 9 patients, and increased in 7 patients. The 2-year actuarial progression-free survival was 91%. Higher maximum dose was statistically related to tumor control (p = 0.027).

Thirty-three patients had adequate clinical follow-up. Among them, 21 patients had improvement in their presenting symptoms, 8 patients were stable after treatment with no worsening of their presenting symptoms, 2 patients developed new symptoms, and 1 patient experienced symptom deterioration. Notably, 1 patient with neurofibromatosis Type 2 developed new symptoms that were unrelated to the tumor treated with Gamma Knife surgery.

Conclusions. Gamma Knife surgery is a reasonably effective treatment option for patients with nonvestibular schwannomas. Patients require careful follow-up for tumor progression and signs of neurological deterioration.

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Key words • nonvestibular schwannoma • Gamma Knife radiosurgery • outcomes

Abbreviations used in this paper: CISS = construction in steady state; CN = cranial nerve; GKS = Gamma Knife surgery.
nonvestibular schwannomas with GKS at the University of Virginia.

**Methods**

**Patient Attributes**

From an institutional review board–approved prospective database, patients with nonvestibular schwannomas undergoing GKS at the University of Virginia were identified and evaluated. Between July 1989 and January 2008, 36 patients with nonvestibular schwannomas were treated with GKS at the University of Virginia (Table 1). Twenty-five of these patients were included in a prior publication from our center. However, all the patients in the previously analyzed trigeminal schwannoma cases had additional data, including neuroimaging and clinical follow-up. The study population comprised 21 female and 15 male patients. The tumor distribution included 25 trigeminal (69.4%), 3 hypoglossal (8.3%), 2 abducent (5.6%), 2 jugular foramen (5.6%), 1 facial (2.8%), 1 trochlear (2.8%), 1 oculomotor (2.8%), and 1 glossopharyngeal (2.6%) schwannomas. In 20 patients the tumors were on the left side, and in 16 they were on the right side.

Two patients had a history of associated neurofibromatosis Type 2. One of these patients had a trigeminal schwannoma on the left side with no neurological symptoms except right foot drop, and the other, who had been treated previously with GKS for a posterior fossa ependymoma and a right-sided trigeminal schwannoma, had a right-sided jugular foramen schwannoma. The median age of the patients was 48 years (mean 45.6 years, range 10–72 years). At the time of GKS, the median tumor volume was 2.9 cm³ (range 0.07–8.8 cm³). Two patients were treated for recurrent tumor growth after prior radiotherapy. Thirteen patients (36%) were treated for residual tumors following resection, while the remaining 23 patients (64%) underwent GKS as an initial treatment on the basis of typical radiographic characteristics and clinical features highly suggestive of nonvestibular schwannomas.

The presenting symptoms of patients with nonvestibular schwannomas were as follows (in order of decreasing frequency): paresthesia in 17 patients, diplopia in 13, motor weakness in 9, headache in 7, pain in 8, disturbance of balance (dizziness/vertigo) in 6, and nausea and vomiting in 3.

**Radiosurgical Technique**

The radiosurgical approach for nonvestibular schwannomas at our center has been previously described. In brief, the Leksell G frame was placed using sterile technique and under monitored anesthesia. Magnetic resonance imaging was performed for target definition in all cases. Contrast-enhanced, thin-slice T1-weighted axial and coronal images were obtained for treatment planning, as well as standard T2-weighted and/or CISS sequences.

Gamma Knife treatment planning was employed using the KULA system, and later Gamma Plan (Elekta AB) treatment planning software. Treatment planning was performed by a team that included a neurosurgeon, a radiation oncologist, and a medical physicist. The schwannoma was contoured and so too were critical structures at risk (for example, the optic apparatus or brainstem). A dose plan was rendered via an iterative process, and blocking of critical structures was performed as needed.

The median number of isocenters used was 5 (range 1–17 isocenters). The median marginal dose was 13.5 Gy (range 9.3–20 Gy), prescribed to a median isodose line of 50% (range 30%–60%). The median maximum dose was 30 Gy (range 21.7–50 Gy). The median tumor volume was 2.9 cm³ (range 0.07–8.8 cm³).

**Follow-Up Procedure**

The response of the tumor after GKS was assessed by means of serial neuroradiological studies. Patients general-

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**TABLE 1: Summary of demographic and clinical characteristics in 36 patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>21 (58)</td>
</tr>
<tr>
<td>female</td>
<td>15 (42)</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>4 (11)</td>
</tr>
<tr>
<td>21–40</td>
<td>11 (31)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>21 (58)</td>
</tr>
<tr>
<td>tumor location</td>
<td></td>
</tr>
<tr>
<td>trigeminal nerve</td>
<td>25 (69)</td>
</tr>
<tr>
<td>hypoglossal nerve</td>
<td>3 (8)</td>
</tr>
<tr>
<td>facial nerve</td>
<td>1 (3)</td>
</tr>
<tr>
<td>trochlear nerve</td>
<td>1 (3)</td>
</tr>
<tr>
<td>oculomotor nerve</td>
<td>1 (3)</td>
</tr>
<tr>
<td>glossopharyngeal nerve</td>
<td>1 (3)</td>
</tr>
<tr>
<td>presenting Sx</td>
<td></td>
</tr>
<tr>
<td>numbness/tingling</td>
<td>17 (47)</td>
</tr>
<tr>
<td>diplopia</td>
<td>13 (36)</td>
</tr>
<tr>
<td>weakness</td>
<td>9 (25)</td>
</tr>
<tr>
<td>headache</td>
<td>7 (19)</td>
</tr>
<tr>
<td>pain</td>
<td>8 (22)</td>
</tr>
<tr>
<td>dizziness/vertigo</td>
<td>6 (17)</td>
</tr>
<tr>
<td>nausea &amp; vomiting</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

* Pts = patients.
ly underwent MR imaging at 6-month intervals for the first 2 years. Subsequently, they underwent annual follow-up MR imaging until 5 years after GKS, and then biennially thereafter. All MR images were reviewed by a neurosurgeon and a neuroradiologist at the University of Virginia. The MR images were evaluated for tumor growth, stability, or regression. Tumors were considered to have regressed if the tumor volume decreased by 15% or more. Tumors were considered to have progressed if the tumor volume increased by 15% or more. Tumors between these limits were regarded as radiologically stable.39

In the current study, all but 1 patient had a minimum follow-up of 1 year. Whenever possible, patients were evaluated for clinical changes by neurosurgeons at the treating center. However, as patients did not always return for clinical evaluations, clinical assessment was made on the basis of notes from referring physicians and direct communications with the patients themselves. Clinical evaluations typically coincided with the times of radiological follow-up. All imaging studies included as part of the assessment of tumor control were directly evaluated by a neurosurgeon and a neuroradiologist at the University of Virginia so as to accurately assess for tumor control.

Statistical Analysis

Progression-free survival and 2-year actuarial survival were calculated with the Kaplan-Meier method. Continuous variables were compared using the t-test. Categorical parameters were compared with the Fisher exact test (R-project, 2010). A binary logistic regression model was used to analyze factors associated with local tumor control. All data were analyzed using a commercial statistical package (SPSS version 19.0; IBM Corp.). All of the comparisons were 2-sided, and a p value < 0.05 was considered statistically significant.

Results

Tumor Response After GKS

The median follow-up time in our cohort was 37 months (mean 54 months, range 2–180 months). Although nearly all patients had a minimum of 12 months of follow-up, 1 patient with 2 months of follow-up was included. That patient had tumor progression at 2 months post-GKS and underwent resection at another university medical center; the patient was included so as not to unfairly bias the radiological follow-up. The 2- and 5-year actuarial progression-free survivals were 91% and 78%, respectively (Fig. 1).

Based on the serial radiological follow-up studies, 20 patients (55.6%), including the 2 patients with neurofibromatosis, had a decrease in tumor size; 9 patients (25%) exhibited stable tumor size, and 7 patients (19.4%) had an increase in tumor size (Fig. 2, Table 2).

A binary logistic regression model was used to analyze factors associated with tumor control. Covariates considered included tumor location (type), maximum dose, and tumor volume. Maximum dose was found to be significantly associated with a higher probability of tumor control (p = 0.027, HR 0.747, 95% CI 0.578–0.967).
Gamma Knife surgery for nonvestibular schwannomas

TABLE 2: Radiological outcomes of nonvestibular schwannoma after GKS in 36 patients

<table>
<thead>
<tr>
<th>Tumor Response</th>
<th>No. of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>decrease</td>
<td>20 (56)</td>
</tr>
<tr>
<td>increase</td>
<td>7 (19)</td>
</tr>
<tr>
<td>stable</td>
<td>9 (25)</td>
</tr>
</tbody>
</table>

Eight patients (22%) did not show improvement but had no further deterioration of their presenting symptoms following GKS; tumor size decreased in 4 of these patients, was unchanged in 2, and increased in 2.

One patient in our series had deterioration of his presenting symptoms during the postradiosurgical follow-up. The patient had a hypoglossal schwannoma and presented with lower- and upper-extremity tremors, paresthesia, slurred speech, right-sided tongue deviation, and drooling. At the time of GKS the tumor volume was 7.9 cm³. His symptoms persisted after GKS. Recently, he lost his speech and ambulation abilities. His last follow-up MR imaging study indicated evidence of an increase in the tumor size.

Two patients with trigeminal schwannoma (5.6%) developed new symptoms following GKS. At the time of GKS, they only complained of unilateral facial paresthesia with no other neurological deficits. They both had chronic headache after GKS, although one subsequently experienced improvement in this symptom during the ensuing follow-up.

No patient died as a result of adverse effects from GKS or tumor progression. One patient died of unrelated causes. Another patient died 5 years after GKS; her last follow-up examination was 1 year before her death and showed a stable tumor. The remaining patients were alive as of the most recent scheduled follow-up.

Discussion

Resection

Historically, surgical intervention has been the standard management for skull base tumors including schwannomas. Schwannomas, however, represent a particular challenge, given that they are in immediate proximity to at least one if not more CNs. Postoperative deficits after resection of vestibular schwannomas and other less common schwannomas have been reported in 8.6%–50% of surgical cases.1,2,8,32,34,36,41,44

For nonvestibular schwannomas, the experience with microsurgery is more limited and the results more heterogeneous than for vestibular schwannomas. Recurrence rates as high as 14% have been noted in modern series. Samii et al.33 reported results in a cohort of 12 patients with solitary trigeminal schwannomas who underwent resection. Of these, 6 patients had some degree of postoperative morbidity including 2 with CSF leakage, 1 with transient quadriplegia, 2 with facial weakness, and 1 with lateral sinus thrombosis. Tumor recurrence or progression was seen in 17% of patients. In another series of 33 patients with trigeminal schwannomas, Day and Fu-

kushimaw observed a recurrence of 3% and new trigeminal deficits of hypesthesia in 6 patients, anesthesia in 5, and motor deficits in 20. Such experiences in the hands of highly competent skull base surgeons underscores the challenges of resection of nonvestibular schwannomas and a scenario in which many patients might consider the cure worse than the underlying disease.

Radiation Therapy

Fractionated radiation therapy has been used in some centers for the treatment of nonvestibular schwannomas. Limited radiation therapy series have been reported in the literature.10,27,38,42,43 Most of these series involve small numbers of patients but shed some light on the effectiveness and safety of fractionated radiation therapy for nonvestibular schwannomas. In 2001, Zabel et al.45 reported on a series of 13 patients who underwent radiotherapy. Their tumor volume ranged from 4.5 to 76 cm³ (median 19.8 cm³). With a median follow-up of 33 months, no patient exhibited new neurological deficits; the tumor control rate was 100%. Recently, another study, reported by Hamm et al.10 in 2008, demonstrated a local tumor control rate of 95% with an average follow-up of 35 months in 19 patients treated with radiotherapy between 1996 and 2007. No new or increased neurological deficit was found in that patient cohort. In a similar study of 24 patients, also published in 2008, Showalter et al.38 reported a tumor control rate of 95%, but there was a short period of follow-up ranging from 1 to 91 months (median 24 months).

Stereotactic Radiosurgery

In the modern era, stereotactic radiosurgery has played an increasingly important role in the treatment of patients with vestibular schwannomas. Radiosurgery offers a minimally invasive alternative to microsurgery. Also, as most intracranial schwannomas are well demarcated and of reasonable volume, radiosurgery has largely replaced radiotherapy for treatment of vestibular and nonvestibular schwannomas. In experienced centers, radiosurgery offers a favorable chance of tumor control and a low risk of CN injury after treatment of a small to moderate volume vestibular schwannoma.32,19,16,24,25

Intracranial schwannomas arising from CNs other than the vestibular-cochlear nerve are much less common. Stereotactic radiosurgery appears to represent a reasonable treatment option for nonvestibular schwannomas (Table 4). In the current series, the 2- and 5-year actuarial progression-free survival times were 91% and

TABLE 3: Summary of clinical outcomes in 33 patients

<table>
<thead>
<tr>
<th>Clinical Condition at FU</th>
<th>No. of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>improved</td>
<td>21 (64)</td>
</tr>
<tr>
<td>no change</td>
<td>8 (24)</td>
</tr>
<tr>
<td>deteriorated Sx</td>
<td>1 (3)</td>
</tr>
<tr>
<td>new Sx</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

* FU = follow-up.
78%, respectively, which are comparable to the trigeminal schwanna radiosurgical series conducted by Kano et al., who reported 1- and 5-year rates of 97% and 82%, respectively.

Similarly, Zhang and colleagues published a study on 27 patients who were treated with the GKS over a 7-year time span. They observed a 96% rate of tumor growth control and 0% rate of resultant neurological deficits over a follow-up period of more than 3 years. In the current study, GKS resulted in an overall tumor control rate of 80.6% of our patients with nonvestibular schwannomas. Moreover, neurological preservation or improvement was demonstrated in 88% of patients.

Management of Nonvestibular Schwannoma

There are, of course, inherent differences in selection criteria, type and length of follow-up, and small patient populations that preclude us from rigorously comparing the 3 treatment options. Nevertheless, there are certain fundamental tenets to the management approach of these lesions. Most nonvestibular schwannomas involve the skull base. They are typically in close proximity to more than one CN and major cerebrovascular structures. Thus, complete microsurgical resection is difficult if not impossible, particularly if the CN function is intact or nearly so at the time of intervention. To be certain, resection still represents an important tool in the neurosurgical armamentarium for these tumors. Resection is most valuable in instances when there is diagnostic uncertainty regarding the tumor etiology, significant mass effect from the tumor and symptoms attributable to the mass effect, or when the tumor is largely composed of a cystic component that would be less responsive or possibly unresponsive to stereotactic radiosurgery. Resection can also be undertaken is patients who show signs of tumor progression after stereotactic radiosurgery.

In the modern era, intracranial schwannomas are being detected at an earlier stage. Consequently, they usually exhibit a small to moderate tumor volume at the time of diagnosis, and such a volume makes them amenable to radiosurgery. They are also well demarcated on MR images. Although they may erode the skull base by pressure or invade the cavernous sinus, they rarely invade the brain parenchyma itself, so the radiation dose to the brain tissue is usually minimal. At our center, external beam radiation therapy has very little role in the management of intracranial, nonvestibular schwannomas. We have generally found stereotactic radiosurgery to be useful for patients harboring such tumors.

Diagnosis can be made with reasonable certainty given the patient’s clinical history and MR imaging features of the tumor. Second on the differential diagnosis for most patients with a radiographically diagnosed schwannoma is a meningioma. Meningiomas tend to be very amenable to radiosurgery also. Therefore, stereotactic radiosurgery represents not just a good treatment option for recurrent or residual nonvestibular schwannomas but also a preferred initial treatment for many patients.

Although differentiation between an intracranial schwannoma and meningioma is achievable in the majority of cases based on the typical clinical features and distinct radiological characteristics, it is possible that the lesions in some of the patients included in the current study were meningiomas. Thus, the results should be interpreted with some degree of caution. A trend has been noted in the literature toward an increased use of radiosurgery as the initial treatment for small- to moderate-size tumors that are clinically and radiographically but not histologically diagnosed as schwannomas. In a study in which radiosurgery was used to treat imaging-diagnosed intracranial meningiomas, the actuarial rate of identifying a diagnosis other than the one they had presumed was 2.3% ± 1.4% at 5 and 10 years. The risk of incorrect diagnosis in the era of MR imaging coupled with consistent clinical history and neurological examination seems low. In the

### TABLE 4: Summary of major series of nonvestibular schwannomas treated by GKS

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Years of Procedure</th>
<th>No. of Pts</th>
<th>Tumor Vol (cm³)</th>
<th>FU (mos)</th>
<th>% Local Tumor Control</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamm et al., 2008</td>
<td>2000–2005</td>
<td>19</td>
<td>14.6±</td>
<td>35†</td>
<td>95</td>
<td>No pt experienced new or worsening Sx</td>
</tr>
<tr>
<td>Kim et al., 2008</td>
<td>7-yr period</td>
<td>8</td>
<td>0.22†</td>
<td>21†</td>
<td>100</td>
<td>No pt experienced new or worsening Sx</td>
</tr>
<tr>
<td>Pollock et al., 2002</td>
<td>1992–2000</td>
<td>23</td>
<td>8.9†</td>
<td>43†</td>
<td>96</td>
<td>1 patient w/ malignant schwannoma had tumor progression &amp; died 4 yrs later; 4 pts (17%) developed radiosurgery-related morbidity</td>
</tr>
<tr>
<td>Nishioka et al., 2009</td>
<td>1994–2006</td>
<td>17</td>
<td>8.2*</td>
<td>59.9†</td>
<td>94</td>
<td>No pt experienced new or worsening Sx</td>
</tr>
<tr>
<td>Pan et al., 2005</td>
<td>1993–2001</td>
<td>56</td>
<td>8.7*</td>
<td>68†</td>
<td>93</td>
<td>4 pts had worsening Sx; trigeminal nerve dysfunction was stable or slightly worse in 13 pts</td>
</tr>
<tr>
<td>Zhang et al., 2002</td>
<td>1993–2000</td>
<td>27</td>
<td>13.5*</td>
<td>38.7†</td>
<td>96</td>
<td>No pt experienced new or worsening Sx</td>
</tr>
<tr>
<td>Hasegawa et al., 2005</td>
<td>1991–2003</td>
<td>37</td>
<td>10*</td>
<td>54†</td>
<td>84</td>
<td>1 pt experienced new symptoms despite the tumor control</td>
</tr>
<tr>
<td>Sheehan et al., 2007</td>
<td>1989–2005</td>
<td>26</td>
<td>3.98†</td>
<td>48*</td>
<td>89</td>
<td>3 pts experienced worsening Sx</td>
</tr>
<tr>
<td>Showalter et al., 2008</td>
<td>1996–2007</td>
<td>15</td>
<td>4†</td>
<td>24†</td>
<td>95</td>
<td>4% of the pts had worsening Sx</td>
</tr>
<tr>
<td>Current series</td>
<td>1989–2008</td>
<td>36</td>
<td>2.9†</td>
<td>37,† 54*</td>
<td>81</td>
<td>3 pts had clinical worsening of Sx</td>
</tr>
</tbody>
</table>

* Mean value. † Median value.
current study, none of the patients who were treated with radiosurgery as an initial treatment and subsequently underwent resection were diagnosed with anything other than a schwannoma.

Radiosurgical doses of 12–15 Gy to the tumor margin accompanied by high conformity and a steep dose gradient afford favorable tumor control. Striving for a higher maximum dose to the tumor appears to improve the long-term rate of tumor control. Moreover, neurological preservation or improvement, particularly of CN function, frequently accompanies radiosurgically induced tumor control of a nonvestibular schwannoma. Stereotactic radiosurgery is a very important part of contemporary tumor control of a nonvestibular schwannoma. Based upon the current study and others available in the literature, radiosurgery is likely to play an expanded role in the future treatment of these patients.

Conclusions

Gamma Knife surgery is a generally effective option for treatment of different CNoI appears high, and preservation or improvement of neurological function is common. Higher maximum dose appears related to improved local tumor control.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sheehan, Xu. Acquisition of data: Sheehan, Elsharkawy, Xu. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Elsharkawy, Xu, Schlesinger. Administrative/technical/material support: Sheehan. Study supervision: Sheehan.

References


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