Linear accelerator radiosurgery for vestibular schwannomas

WILLIAM A. FRIEDMAN, M.D., PATRICK BRADSHAW, M.S., ADAM MYERS, B.S., AND FRANK J. BOVA, PH.D.

Department of Neurosurgery, University of Florida, Gainesville, Florida

Object. Radiosurgery has become a popular treatment for small vestibular schwannomas (VSs). The aim of this study was to review an extensive, single-institution experience with linear accelerator (LINAC) radiosurgery for VSs.

Methods. Between July 1988 and August 2005, 390 patients with VSs were treated with LINAC–based radiosurgery at the authors’ institution. Patient and treatment variables were prospectively maintained in a computer database. Outcomes were tracked through periodic clinical examinations and annual scanning studies. Multivariate and actuarial statistics were used to analyze rates of local tumor control and complications, including facial and trigeminal neuropathies, after treatment.

One- and 2-year actuarial control rates were both 98%, and the 5-year actuarial control rate was 90%. Only four patients (1%) required surgery for tumor growth. Seventeen patients (4.4%) reported facial weakness and 14 patients (3.6%) reported facial numbness after radiosurgery. The risk of these complications rose with increasing tumor volume or increasing radiosurgical dose to the tumor periphery. Since 1994, when doses were deliberately lowered to 1250 cGy, only two patients (0.7%) have experienced facial weakness and two (0.7%) have experienced facial numbness.

Conclusions. Radiosurgery provides a safe and effective therapeutic alternative to surgery for small VSs.

KEY WORDS • vestibular schwannoma • radiosurgery • linear accelerator

Among benign intracranial tumors, VS (acoustic neuroma) has been one of the most frequent targets for SRS. This tumor type, which represents approximately 15% of all primary brain lesions, is a benign proliferation of Schwann cells arising from the myelin sheath of the vestibular branches of the eighth cranial nerve. It is slightly more common in women, who present at a mean age of 50 years, and occurs bilaterally in patients with neurofibromatosis Type 2.

Leksell first used SRS to treat a VS in 1969. It is a logical alternative treatment modality for this tumor type for several reasons. A VS is typically well demarcated from surrounding tissues on neuroimaging studies. The sharp borders of this noninvasive tumor make it a suitable match for the characteristically steep dose gradient produced at the boundary of a radiosurgical target, which allows the radiosurgeon to minimize radiation to normal tissue. Excellent spatial resolution on Gd-enhanced MR imaging facilitates radiosurgical dose planning. These tumors typically occur in an older population that may be less fit for microsurgical removal under general anesthesia. Finally, the location of these tumors at the skull base in proximity to multiple critical neurological structures (that is, cranial nerves and brainstem) leads to appreciable surgical morbidity and infrequent death even in expert hands. These factors make the concept of an effective, less invasive, less morbid alternative treatment that can be performed in a single day under local anesthesia extremely attractive.

In this paper we review our experience at the University of Florida with LINAC radiosurgery for VSs.

Clinical Material and Methods

Study Design

We performed a retrospective analysis of all patients who had been treated with LINAC-based radiosurgery for VS between July 1988 and August 2005. Three hundred ninety patients were treated during the study interval. Patient variables were entered into a computerized database at the time of treatment, and response to therapy was updated at regular 1-year intervals. The variables included age, side of lesion, previous surgery, von Recklinghausen disease, documented prior tumor growth, treatment isodose volume, and radiation dose. Hearing function was not systematically evaluated or followed up. Clinical evaluations and imaging studies were conducted during the follow-up period. All images were reviewed by the senior author (W.A.F.) and were visually compared with the radiosurgical dose planning images. Patients or referring physicians were interviewed by telephone to confirm clinical status when such information was not available from clinic visits at the University of Florida.
Patient Characteristics

Of the 390 patients, 182 were men and 208 were women, and the median age was 62 years (range 19–88 years). One hundred eighty-seven tumors were on the left side and 203 were on the right. One hundred thirty-three tumors had documented growth before radiosurgery; 257 had no documented growth. Eighty patients had undergone previous surgery. The median treatment isodose volume was 2.2 cm³ (range 0.2–22.4 cm³). The mean duration of the follow up was 40 months, although 63 patients were followed up for more than 5 years.

Radiosurgical Treatment

All patients were treated using the University of Florida radiosurgery system. The treatment paradigm has been described in several previous publications.6,7 Briefly, the patients underwent clinical evaluation and MR imaging the day before treatment. Once a local anesthetic agent had been applied and a head ring placed on the patient, stereotactic computed tomography was performed. Previously obtained MR images were fused with the stereotactic computed tomography scans, and dosimetry planning was performed. The goal of planning was to provide a highly conformal dose distribution. After treatment the patients were briefly observed and then discharged home.

The median SRS dose to the target periphery was 1250 cGy (range 1000–2250 cGy). Since 1994 almost all tumors have been treated with the 1250-cGy dose. Rarely, 1000 cGy was prescribed for larger tumors. All lesions were treated to the 70 or 80% isodose line. The number of isocenters used varied from one to 14. The majority of patients were treated using either one (114 patients) or two (154 patients) isocenters, with a tendency toward more isocenters and greater conformality in the later years of this study.

Definition of Outcomes

The following outcomes were identified and analyzed: local control, facial weakness, facial numbness. Local control was defined as unsuccessful if the last follow-up imaging study showed any tumor enlargement. Facial weakness and numbness were defined as new deficits occurring any time after radiosurgery, regardless of the degree or permanence.

Statistical Analysis

The Cox proportional-hazards regression was used to relate prior surgery, age at treatment, side of lesion, prior tumor growth, tumor volume, and radiation dose to the duration of local control. The proportional-hazards assumption was assessed using a test of the Schoenfeld residuals; we report hazard ratios, probability values, and 95% CIs. In analyzing the two complication variables (numbness and weakness), logistic regression was used to determine whether any of the explanatory variables plus an indicator for von Recklinghausen disease were associated with outcome; we report ORs, probability values, and 95% CIs.

In the Cox and logistic regression models, a patient’s age at treatment, tumor volume, and radiation dose (scaled so unit increases corresponded to 250-cGy increments) were included as continuous covariates. Note that in the stratified Cox model, quintiles of age were used as stratification groups. Indicator variables were used for prior surgery, side of lesion (indicating the left side), prior tumor growth (indicating the presence of prior growth); for the logistic models, indicator variables were used for von Recklinghausen disease. We intended to include dose as a categorical predictor; however, small cell sizes and no events (failure of local control) in the upper dose categories precluded this strategy.

Parameters were deemed to be statistically significant when the probability value was less than 0.05. Statistical analysis was conducted using commercially available software (Stata, version 8.0; Stata Corp., College Station, TX).

Results

Tumor Control

Local control data were available in 295 patients; 42 patients were lost to follow up; and the remainder have yet to undergo follow-up scanning. Actuarial local tumor control was 98% at 1 and 2 years, and 90% at 5 years (Table 1 and Fig. 1). Actuarial local control remained 90% at 10 years, but only 10 patients were followed up to that point. None of the variables was significantly associated with local control. Although 13 patients exhibited tumor enlargement during the follow-up evaluation, only four tumors (1%) enlarged to the point that surgical treatment was required. Thus, 99% of the patients treated to date have required no surgical intervention.

Facial Weakness

Among the 390 patients, 17 (4.4%) experienced new facial weakness after treatment. Only two (0.7%) of the 296 patients treated with the 1250-cGy dose or lower have experienced this complication. Tumor volume was significantly associated with facial weakness, with each cubic centimeter rise in volume increasing the odds of facial weakness by 17%. The prescribed dose showed a significant association as well, with each 250-cGy dose increase resulting in 8.14 times the odds of facial weakness (Table 2).

Facial Numbness

Of the 390 patients, 14 (3.6%) experienced facial numbness. Only two (0.7%) of 296 patients treated with the 1250-cGy dose or lower have experienced this complication. Results of a logistic regression analysis showed that tumor volume and radiation dose were independently correlated with this complication (Table 3).

Discussion

Linear Accelerator–Based Radiosurgery: Previous Reports

The published writings on LINAC-based radiosurgery for the treatment of VSs is relatively limited compared with the Gamma Knife literature.5,10,12 At the University of Florida, Foote and colleagues’ performed an analysis of the risk factors associated with radiosurgery for VSs. The aim of that study was to identify factors associated with delayed cranial neuropathy after radiosurgery for VS and to determine how such factors can be manipulated to minimize the incidence of radiosurgical complications while maintaining high rates of tumor control. Between July 1988 and June 1998, 149 cases of VSs were treated using LINAC radiosur-
Radiosurgery for vestibular schwannomas

**TABLE 1**

<table>
<thead>
<tr>
<th>Time (yrs)</th>
<th>No. of Patients</th>
<th>No. of Treatment Failures</th>
<th>Survivor Function</th>
<th>SEM</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>241</td>
<td>4</td>
<td>0.98</td>
<td>0.0075</td>
<td>0.96–0.99</td>
</tr>
<tr>
<td>2</td>
<td>194</td>
<td>2</td>
<td>0.98</td>
<td>0.0100</td>
<td>0.95–0.99</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>9</td>
<td>0.90</td>
<td>0.0273</td>
<td>0.83–0.94</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0.90</td>
<td>0.0273</td>
<td>0.83–0.94</td>
</tr>
</tbody>
</table>

* SEM = standard error of the mean.

---

14 Gy. After a mean follow-up period of 32 months (range 12–60 months), 98% of the tumors were controlled. The actuarial hearing preservation rate was 71%. New transient facial neuropathy developed in 24% of the patients and persisted to a mild degree in 8%. The radiation dose correlated significantly with the incidence of cranial neuropathy, particularly in large tumors \( (\geq 4 \text{ cm}^3) \).

Several reports on smaller series of patients treated with LINAC-based radiosurgery for VSs have been published in recent years. Martens and associates\(^\text{13}\) reported on 14 patients with at least 1 year of follow up after radiosurgery in the LINAC unit at the University Hospital Ghent, Belgium. A mean tumor margin dose of 19.4 Gy (range 16–20 Gy) was delivered to the 70% isodose line with a single isocenter. The mean duration of follow up was 19 months (range 12–24 months). During this relatively short follow-up interval, 100% radiographically demonstrated tumor control was achieved: 29% of the tumors regressed, 71% remained stable, and none enlarged. The rates of delayed facial and trigeminal neuropathy were 21 and 14%, respectively, and two of three facial nerve deficits resolved. Preoperative hearing was preserved 50% of the time.

Valentino and Raimondi\(^\text{16}\) reported on 23 patients who had been treated with LINAC radiosurgery in Rome, Italy. Five of these patients had neurofibromatosis and seven (30%) underwent previous surgery. The total radiation dose to the tumor margin ranged from 12 to 45 Gy (median 30 Gy) and was delivered in one to five sessions. One or two

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>SEM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>prior surgery</td>
<td>3.77</td>
<td>2.99</td>
<td>0.09</td>
</tr>
<tr>
<td>patient age</td>
<td>0.99</td>
<td>0.02</td>
<td>0.65</td>
</tr>
<tr>
<td>VRD</td>
<td>0.64</td>
<td>0.77</td>
<td>0.71</td>
</tr>
<tr>
<td>side of lesion</td>
<td>0.45</td>
<td>0.29</td>
<td>0.22</td>
</tr>
<tr>
<td>prior tumor growth</td>
<td>3.75</td>
<td>3.09</td>
<td>0.11</td>
</tr>
<tr>
<td>treatment isodose vol</td>
<td>1.17</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>radiation dose</td>
<td>8.14</td>
<td>3.55</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* VRD = von Recklinghausen disease.
and Barcia (medi-treated 80 consecutive patients consisting of J. Neurosurg. / Volume 105 / November, 2006

...normal facial nerve function was preserved in all cases. Two cases of new trigeminal nerve dysesthesia required medication.

Weaknesses of This Study

The following factors represent limitations of the present study. For logistic reasons, hearing preservation was not systematically studied. The senior author (W.A.F.), rather than an uninvolved objective reviewer, compared treatment and follow-up images. Data on patients lost to follow up or without radiographic follow up could have skewed the results. Very few patients have been followed up to the 10-year point. Actuarial data are only reliable to 5 years.

Conclusions

In this study we documented excellent actuarial control rates at 1, 2, and 5 years after radiosurgery. Preliminary 10-year data suggest that the results are durable. Only 1%

\[ \text{isocenters were used, and the mean duration of follow up was 40 months (range 24–46 months). Results using this less conventional method of multisession radiosurgery were comparable to findings after other radiosurgical techniques. Tumor control was achieved in 96% of the patients: the tumor regressed in 38%, remained stable in 58%, and enlarged in 4%. Facial and trigeminal neuropathies each occurred at a rate of 4%, and "hearing was preserved at almost the same level as that prior to radiosurgery in all patients."}

\[ \text{The use of LINAC radiosurgery for acoustic lesions is briefly discussed in reports by Delaney, et al., and Barcia Salorio, et al.} \]

\[ \text{Fractionated Radiosurgery} \]

Although some would reject the term “fractionated radiosurgery,” a number of groups have used multiple-session treatments in an attempt to reduce complications, especially hearing loss. Varlotto and colleagues treated 12 patients with VS between June 1992 and October 1994. The follow-up period ranged from 16 to 44 months. The patient age ranged from 27 to 70 years (median 45 years). Eight patients were treated with primary stereotactic radiotherapy, and four patients were treated after primary surgical intervention for recurrent (three patients) or persistent (one patient) disease. Tumor volumes were 1.2 to 18.4 cm\(^3\) (median 10.1 cm\(^3\)). Tumors received 1.8 Gy radiation every day, normalized to the 95% isodose line. Patients received a minimum prescribed dose of 54 Gy in 27 to 30 fractions during a 6-week period. After a median follow up of 26.5 months, local control was achieved in 12 of 12 lesions. Tumor regression was noted in three patients, and tumor stabilization occurred in the remaining nine. No new cranial nerve deficits developed in any patient. One patient suffered worsening of preexisting trigeminal neuropathy, and another experienced a decrease in hearing. However, all nine patients with useful hearing before stereotactic radiotherapy retained useful hearing at the last follow up.

Fuss and colleagues treated 51 patients with VS by using conventional fractionation. The mean total dose was 57.6 ± 2.5 Gy. Forty-two patients were followed up for at least 12 months and included in an outcome analysis. The mean follow up was 42 months. Actuarial 2- and 5-year tumor control rates were 100 and 97.7%, respectively. The actuarial rate of useful hearing preservation was 85% at both 2 and 5 years. New hearing loss was diagnosed in four patients with neurofibromatosis Type 2. Pretreatment normal facial nerve function was preserved in all cases. Two cases of new trigeminal nerve dysesthesia required medication.

\[ \text{Williams treated 80 consecutive patients consisting of 45 males and 35 females, with a mean age of 56.8 ± 1.7 years. A prospective schedule permitted increased fractionation according to lesion size. Seventy patients having a VS smaller than 3 cm in diameter received five daily fractions of 5 Gy (total 25 Gy), and 10 patients having a VS 3 cm or larger received 10 daily fractions of 3 Gy (total 30 Gy). All treatments were prescribed to the 80% isodose line and administered via the dedicated 10-MV accelerator. For both the larger and smaller VSs, the percentage decrease in volume was similar. No tumor increased in size, facial weakness occurred in no patients, and hearing was preserved in all patients.}

Andrews and colleagues compared the results in patients treated using Gamma Knife surgery with those in patients treated using fractionated radiotherapy between October 1994 and August 2000. The Gamma Knife technique involved a fixed-frame, multiple-shot, high-conformality single treatment, whereas the LINAC technique involved daily conventional fraction treatments involving a relocatable frame, fewer isocenters, and lower conformality. Sixty-nine patients were treated using the Gamma Knife, and 56 patients were treated using radiotherapy. Three patients were lost to follow up; in the remaining 122 patients, the mean follow up was 119 ± 67 weeks in those who received SRS and 115 ± 96 weeks in those who received stereotactic radiotherapy. Tumor control rates were high (≥ 97%) for sporadic tumors in both groups. Cranial nerve morbidities were comparably low in both groups, with the exception of functional hearing preservation, which was 2.5-fold higher in patients who had received conventional fractionation.

Most recently, Chang and colleagues reported on 61 patients treated with the CyberKnife and followed up for at least 36 months. These patients received either 18 or 21 Gy in three fractions. Only one treated tumor progressed. Among the patients who had serviceable hearing, 74% maintained it. No new trigeminal or facial complications developed.

We did not address hearing preservation in the present study. Nonetheless, the rates of facial and trigeminal neuropathy have been exceedingly low since adopting the 1250-cGy dose in 1994. We plan to continue single-fraction treatments (radiosurgery) until data from longer follow-up studies in greater numbers of patients receiving fractionated radiotherapy convincingly demonstrate an advantage in tumor control or complication reduction.

\[ \text{TABLE 3} \]

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>SEM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>prior surgery</td>
<td>4.83</td>
<td>4.38</td>
<td>0.08</td>
</tr>
<tr>
<td>patient age</td>
<td>1.05</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>VRD</td>
<td>1.85</td>
<td>2.46</td>
<td>0.64</td>
</tr>
<tr>
<td>side of lesion</td>
<td>0.45</td>
<td>0.32</td>
<td>0.27</td>
</tr>
<tr>
<td>prior tumor growth</td>
<td>4.54</td>
<td>4.47</td>
<td>0.12</td>
</tr>
<tr>
<td>treatment isodose vol</td>
<td>1.28</td>
<td>0.10</td>
<td>0.00*</td>
</tr>
<tr>
<td>radiation dose</td>
<td>7.38</td>
<td>3.61</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

* Statistically significant.
of patients have required subsequent surgical intervention. Documented tumor growth before radiosurgery had no effect on long-term local control. Reducing the radiosurgical dose to 1250 cGy has had no statistically significant effect on tumor control rates, and thus since 1994 we have used a 1250-cGy treatment dose. Facial weakness or numbness has occurred in 0.7% of patients treated since then.

References