

## Results of acoustic neuroma radiosurgery: an analysis of 5 years' experience using current methods

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**Object.** The goal of this study was to define tumor control and complications of radiosurgery encountered using current treatment methods for the initial management of patients with unilateral acoustic neuroma.

**Methods.** One hundred ninety patients with previously untreated unilateral acoustic neuromas (vestibular schwannomas) underwent gamma knife radiosurgery between 1992 and 1997. The median follow-up period in these patients was 30 months (maximum 85 months). The marginal radiation doses were 11 to 18 Gy (median 13 Gy), the maximum doses were 22 to 36 Gy (median 26 Gy), and the treatment volumes were 0.1 to 33 cm<sup>3</sup> (median 2.7 cm<sup>3</sup>).

The actuarial 5-year clinical tumor-control rate (no requirement for surgical intervention) for the entire series was 97.1 ± 1.9%. Five-year actuarial rates for any new facial weakness, facial numbness, hearing-level preservation, and preservation of testable speech discrimination were 1.1 ± 0.8%, 2.6 ± 1.2%, 71 ± 4.7%, and 91 ± 2.6%, respectively. Facial weakness did not develop in any patient who received a marginal dose of less than 15 Gy (163 patients). Hearing levels improved in 10 (7%) of 141 patients who exhibited decreased hearing (Gardner–Robertson Classes II–V) before undergoing radiosurgery. According to multivariate analysis, increasing marginal dose correlated with increased development of facial weakness ( $p = 0.0342$ ) and decreased preservation of testable speech discrimination ( $p = 0.0122$ ).

**Conclusions.** Radiosurgery for acoustic neuroma performed using current procedures is associated with a continued high rate of tumor control and lower rates of posttreatment morbidity than those published in earlier reports.

**KEY WORDS** • radiosurgery • stereotaxis • acoustic neuroma • vestibular schwannoma • radiation complication

**R**ADIOSURGERY is an alternative to microsurgical resection of acoustic neuroma (vestibular schwannoma) and is associated with lower patient morbidity and comparable long-term tumor-control rates.<sup>6,11,13–15,17</sup> An analysis of our first 5 years of experience with radiosurgery of acoustic neuromas, which was performed using marginal tumor doses on the order of 16 Gy, revealed significant rates of subsequent facial weakness (21%), facial numbness (27%), and decreased hearing (49%).<sup>11</sup> We subsequently modified our radiosurgical method in two major ways. First, we decreased the marginal tumor-dose prescriptions to reduce complications. Second, treatment procedures were improved to include high-resolution stereotactic MR imaging, as well as faster, more sophisticated user-friendly radiosurgical planning that included more isocenters to achieve greater conformity and sharper dose falloff.<sup>5,10</sup> In this study we sought to define outcomes of stereotactic radiosurgery when performed using current methods as the primary treatment for acoustic neuroma. We sought to test the hypothesis that the current radiosurgical procedures, including better image definition, more conformal treatment plans, and lower marginal tumor doses (to an average of 13 Gy), re-

duce complications while maintaining a high rate of tumor control.

### Clinical Material and Methods

One hundred ninety patients underwent stereotactic radiosurgery at the University of Pittsburgh between August 1992 and August 1997 for previously untreated unilateral acoustic neuromas. The median follow-up period was 30 months (maximum 85 months). More than 1 year of follow-up MR imaging was conducted in 147 patients and more than 1 year of follow-up clinical examinations in 159 patients. The median patient age was 62 years (range 23–84 years). One hundred two patients were men and 88 were women. Results of audiography were evaluated according to the Gardner–Robertson classification.<sup>7</sup> Before undergoing radiosurgery, 48 patients had Class V hearing, 48 had no testable speech discrimination, and 34 had no hearing, as tested by pure tone average.

Radiosurgery was performed using a gamma knife (Leksell model U in 138 patients and model B in 52 patients [Elekta, Atlanta, GA]). We recorded the age of the cobalt sources at the time of each procedure to assess dose-rate effects. The cobalt source age varied from 0 to 9

*Abbreviation used in this paper:* MR = magnetic resonance.

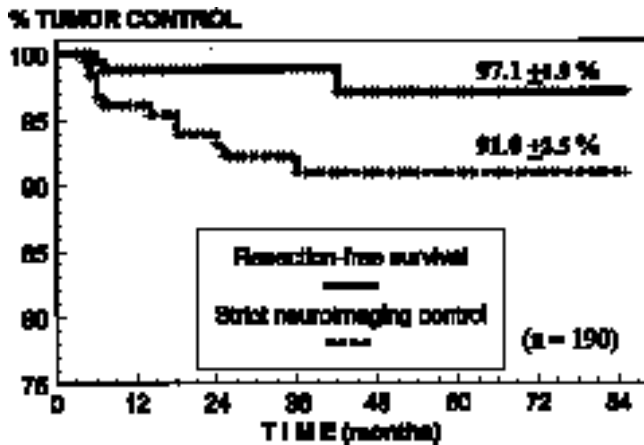


FIG. 1. Graph demonstrating actuarial tumor control for 190 patients who underwent stereotactic radiosurgery for previously untreated unilateral acoustic neuromas. Clinical tumor control or resection-free survival was defined as the absence of significant or sustained tumor growth not requiring surgery. Neuroimaging-determined tumor control was defined as the absence of any documented 1- to 2-mm change in tumor diameter on MR images (including temporary changes), whether it was sustained or required surgical intervention.

years (median 6.3 years). We used stereotactic MR imaging for target definition in all cases. The marginal tumor dose varied from 11 to 18 Gy (median 13 Gy) and maximum dose varied from 22 to 36 Gy (median 26 Gy). The marginal tumor dose was prescribed to the 50% isodose volume in 179 patients, 40% in one patient, 55% in five patients, and 60% isodose volume in five patients. The number of isocenters used per patient varied from one to 13 (median six). Tumor volume varied from 0.1 to 33 cm<sup>3</sup> (median 2.7 cm<sup>3</sup>). Transverse tumor diameter (intracanalicular plus extracanalicular) varied from 0.4 to 5.2 cm (median 1.9 cm). Early in this series, marginal doses of 13 Gy or less were prescribed only for large tumors, whereas in later years 13 Gy became the usual marginal dose for all patients. Because of this policy, patients who received marginal doses of 13 Gy or less (101 patients) had significantly larger transverse tumor diameters (median 1.96 cm compared with 1.69 cm,  $p = 0.0087$  by t-test) than those treated with 14 Gy or higher (89 patients).

#### Statistical Analysis

Tumor control was assessed in two ways. Using the results of neuroimaging, tumor progression was defined strictly as any temporary or sustained increase in tumor diameter measuring at least 1 mm in two dimensions or 2 mm in any direction. Because in most patients tumors that increase in size slightly postradiosurgery either stabilize or shrink afterwards, we also assessed freedom from resection, which appears to be a more reliable indicator of long-term tumor control.<sup>11</sup> Trigeminal neuropathy (facial numbness) was defined as any temporary or permanent, subjective or objective decrease in facial sensation documented by either patient interview or physical examination. Facial neuropathy (facial weakness) was defined as any decrease in facial nerve function as documented by a decrease in the House–Brackmann grade.<sup>8</sup>

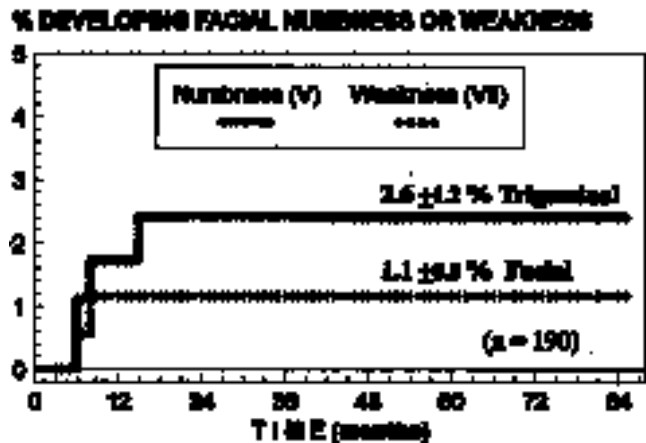


FIG. 2. Graph showing actuarial rates of developing facial numbness (trigeminal neuropathy) or facial weakness after radiosurgery for acoustic neuroma in 190 patients.

The Kaplan–Meier product-limit method<sup>9</sup> was used to calculate actuarial rates of tumor control and freedom from cranial neuropathies for assessable patients. Univariate comparisons of survival between patient groups were performed using the log-rank test.<sup>16</sup> Stepwise multivariate analysis was performed using the Cox proportional hazards model, with all treatment parameters included as continuous variables.<sup>2</sup>

All patients gave informed consent to participate in this retrospective study, which was approved by the University of Pittsburgh Institutional Review Board.

## Results

### Tumor Control

Three patients underwent resection 6, 7, and 42 months after radiosurgery. Significant tumor growth was documented in one of the patients. Another patient moved to a foreign country and underwent resection, according to relatives; however, no details were available. In the third patient a trapped subarachnoid fluid cyst developed adjacent to the tumor. Although the tumor was stable in size after radiosurgery, a subtotal tumor resection was performed with excision of the cyst. The actuarial 5-year clinical tumor-control rate (freedom from resection) for the entire series was 97.1  $\pm$  1.9% (Fig. 1). Freedom from the need for resection was not significantly different ( $p = 0.4306$ ) according to marginal dose (99 of 101 patients or a 97.9% actuarial rate in patients who received a marginal dose of  $\leq$  13 Gy compared with 88 of 89 patients or a 97.6% actuarial rate in patients who received a marginal dose of  $\geq$  14 Gy).

In addition to the three patients who later required resection, temporary or permanent tumor diameter increases of 1 to 2 mm were identified in 10 other patients (13 of 190 patients). In one patient the tumor has shrunk to below the size measured at initial treatment, whereas in the other patients the tumors have so far remained stable in size. Based strictly on the results of neuroimaging studies, the 5-year actuarial tumor-control rate (including 1-mm temporary increases in average diameter as failures) was 91  $\pm$  2.5% (Fig. 1). There was no significant difference

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( $p = 0.7598$ ) in neuroimaging-determined tumor control between marginal doses (94 of 101 or a 90.9% actuarial rate in patients who received a marginal dose of  $\#$  13 Gy compared with 83 of 89 patients or a 91.4% actuarial rate in patients who received a marginal dose of  $\$$  14 Gy).

### Tumor Response

Tumor shrinkage was documented in 51 (35%) of 147 patients in whom follow-up images were obtained for longer than 1 year. There was no significant difference ( $p = 0.994$ , chi-square test) in rates of tumor shrinkage between patients with tumors receiving a dose of 13 Gy or less (26 [35%] of 75 patients) and those receiving a dose of 14 Gy or more (25 [35%] of 72 patients).

### Trigeminal Neuropathy

Trigeminal neuropathy (defined as any temporary or permanent subjective decrease in sensation within the ipsilateral trigeminal nerve distribution) developed in four of 190 patients, 5 to 15 months postradiosurgery, for a 5-year actuarial incidence of 2.6  $\pm$  1.2% (Fig. 2). Facial numbness was accompanied by hypersensitivity or pain in two patients, with both symptoms resolving completely in one patient after a short course of corticosteroid medications. Of the two patients with decreased facial sensation but no hypersensitivity or pain, one achieved complete return of facial sensation 13 months after onset of the deficit (20 months postradiosurgery). Two other patients experienced transient (1 week–1 month) headaches or a pressure sensation in the jaw with no facial numbness at 12 and 15 months; neither of these symptoms was believed to indicate trigeminal neuropathy. Three patients were noted to have ipsilateral, typical tic-type facial pain, without numbness, at their last follow-up examination 16, 48, and 59 months after radiosurgery (marginal dose 12, 13, and 14 Gy with extracanalicular transverse diameters of 12, 29, and 15 mm, respectively) with pain subsequently controlled by a regimen of carbamazepine.

### Facial Neuropathy

Facial neuropathy (defined as a temporary or permanent decline in House–Brackmann facial nerve grade) developed in two of 192 patients, 6 and 8 months postradiosurgery, for a 5-year actuarial incidence of 1.1  $\pm$  0.8% (Fig. 2). Facial weakness occurred with facial numbness in two of the patients counted earlier as having trigeminal neuropathy. These patients both received marginal doses of 15 Gy and maximum doses of 30 Gy. One patient experienced only mild facial asymmetry that was not present at rest (Grade II), whereas the other displayed asymmetry at rest that improved to Grade II after starting a brief course of corticosteroid medications. The actuarial rates for facial weakness in patients who had received a marginal dose of 13 Gy or lower was 0% (zero of 101 patients) compared with 2.5  $\pm$  1.2% (two of 89 patients) who received a dose of 14 Gy or higher (Fig. 3). No patient who received a margin dose that was lower than 15 Gy (161 patients) experienced facial weakness.

### Hearing Preservation

Before undergoing radiosurgery, the hearing levels of

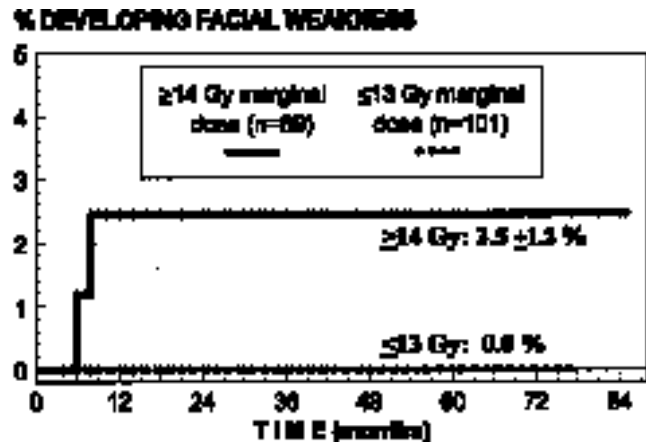


FIG. 3. Graph showing a comparison of actuarial freedom from developing facial weakness (facial neuropathy) after radiosurgery for acoustic neuroma in patients who received marginal tumor doses of 13 Gy or less compared with those who received doses of 14 Gy or more.

the patients, assessed using the Gardner–Robertson scale, were as follows: Class I (normal) in 49 patients, Class II in 27, Class III in 51, Class IV in six, and Class V (no speech discrimination) in 57 patients. Gardner–Robertson hearing levels improved in 10 (7%) of 141 patients who had decreased (Classes II–V) hearing before radiosurgery. Hearing improved from Class III to Class I in three patients, from III to II in one, from IV to II in one, and from IV to III in one. Of the four patients with Class V hearing before radiosurgery who later displayed improvement, hearing improved to Class I in two patients and to Class III in two patients.

Hearing preservation after radiosurgery was classified in three different ways. Hearing levels (measured according to Gardner–Robertson hearing class) were preserved in 103 of 133 assessable patients (with Classes I–IV preoperative hearing), for a 5-year actuarial hearing-level preservation rate of 71  $\pm$  4.7% (Fig. 4). Serviceable hearing (Classes I–II) was preserved in 61 of 75 assessable patients with Class I or II preoperative hearing for a 5-year actuarial preservation rate of 73.5  $\pm$  4.9% (Fig. 4). Preservation of any testable speech discrimination (Class IV or better) was accomplished in 123 of 137 patients, for a 5-year actuarial speech-discrimination preservation rate of 91  $\pm$  2.6% (89.2% in patients who received a marginal dose of  $\#$  13 Gy compared with 86.3% in patients who received a marginal dose of  $\$$  14 Gy).

### Multivariate Analysis

Stepwise multivariate analyses of the effects of radiosurgery on the fifth, seventh, and eighth cranial nerves (decreases in Gardner–Robertson hearing level) were performed using the Cox proportional hazards model. The treatment variables tested included the following: marginal dose (minimum tumor dose), length of nerve that was irradiated (represented by transverse tumor diameter), percentage of isodose volume that was treated, treatment volume, age of the cobalt sources, and predicted rate of facial, trigeminal, or auditory neuropathy based on previous studies.<sup>4</sup> Results of a previous analysis showed that cranial

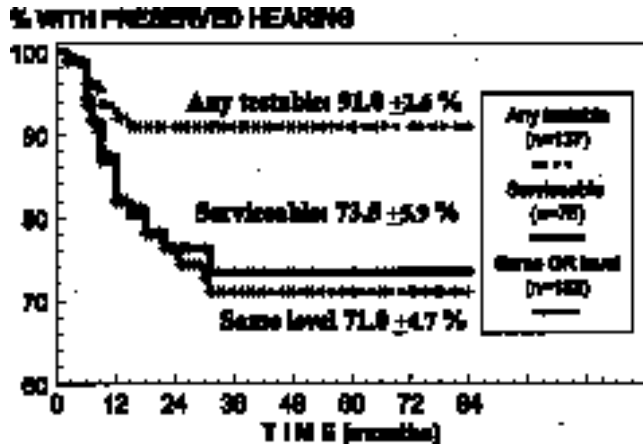


FIG. 4. Graph depicting actuarial hearing preservation rates postradiosurgery in 137 patients who had testable hearing (Gardner–Robertson [GR] Class I–IV) before radiosurgery for acoustic neuroma (75 assessable patients with Class I–II hearing). Hearing preservation was classified as any testable speech discrimination remaining, serviceable hearing (Gardner–Robertson Class I–II) remaining, and preservation of the same Gardner–Robertson hearing level.

neuropathies were best correlated using the length of the irradiated nerve represented by the extracanalicular transverse tumor diameter (a) for the trigeminal nerve and the combined extracanalicular plus intracanalicular midporus transverse tumor diameter (a + y) for the facial and auditory nerves.<sup>4,5,12</sup>

Table 1 summarizes the results of multivariate analyses of the development of postradiosurgery facial, trigeminal, and auditory neuropathies. Multivariate analyses revealed that an increasing marginal tumor dose correlated with increased risk of developing facial weakness ( $p = 0.0342$ , hazards rate ratio 2.46/Gy, 95% confidence interval 1.07–5.65/Gy). Increasing marginal tumor dose also correlated with decreased preservation of testable speech discrimination ( $p = 0.0122$ , hazards rate ratio 0.57/Gy, 95% confidence interval 0.37–0.88/Gy). No variables significantly correlated with preservation of Gardner–Robertson hearing levels or with development of facial numbness. The length of nerve that was irradiated (transverse tumor diameter) did not correlate with risks of facial, trigeminal, or auditory neuropathy in this study.

No other significant complications, aside from those mentioned in the preceding paragraphs, were identified in this study.

## Discussion

Treatment procedures in radiosurgery have evolved over the last 12 years, resulting in a decrease in complications. These changes have included a purposeful deescalation of prescribed doses (marginal tumor doses), the introduction of MR imaging–based treatment planning, and improvements in treatment-planning software that have facilitated the use of more elaborate multiple isocenter treatment plans with improved conformality. Reports of radiosurgery of acoustic neuromas that include patients treated from 1987 to 1991 are important for evaluating

long-term tumor control, but do not reflect the lower risks of morbidity associated with current procedures.<sup>5,11</sup> The reduction in marginal doses used for more recently treated patients raises three important questions that we sought to address in this paper. First, did the use of a lower marginal dose lead to a decrease in tumor control? Second, how much did the use of lower marginal doses reduce complications? Third, should prescribed doses (marginal doses) be reduced even further?

Our evaluation of tumor control in patients treated using lower doses and modern radiosurgical methods was favorable in this series. We had previously found that the most appropriate representation of tumor control is freedom from tumor resection because tumors controlled by irradiation may undergo small increases in tumor diameter from tumor capsule expansion associated with central tumor death.<sup>5,11</sup> The actuarial 5-year clinical tumor-control rate (no requirement for surgical intervention) for the current series (median dose 13 Gy) was 97.1  $\pm$  1.9% (187 of 190 patients, including one patient who underwent tumor resection despite no tumor growth). This compares with a long-term resection-free clinical tumor-control rate of 98% (162 of 166 patients) among patients treated in our first 5 years of experience (median dose 16 Gy).<sup>5,11</sup> Although the follow-up period in the current series is not as long as that in the earlier study, the comparison seems reasonable because all instances of tumor progression requiring resection occurred during the first 3 years of the follow-up period in both series. Within the present series there was no significant difference in tumor control between those patients who received a marginal dose of 13 Gy or less (99 of 101 patients) and those who received a dose of 14 Gy or more (88 of 89 patients). We also used neuroimaging studies for rigorous determination of tumor-control rates (including temporary increases of 1 mm in diameters as failure) to ascertain whether there were any differences according to dose, despite the fact that this parameter poorly represents the true rate of long-term tumor control. The neuroimaging-determined tumor-control rate of 91  $\pm$  2.5% observed in this series is similar to the 89.2  $\pm$  6% rate reported in an analysis of patients treated during our earlier experience with a median dose of 17 Gy.<sup>5,11</sup> Within this current series we found no evidence of decreased tumor control on results of neuroimaging studies between patients who received marginal doses of 13 Gy or lower (94 of 101 patients) and those who received doses of 14 Gy or more (83 of 89 patients). Although additional long-term studies of acoustic neuroma radiosurgery performed using marginal doses of 13 Gy or lower are needed, it does not appear that tumor control has decreased at all compared with the results of older series in which higher-dose radiosurgery was used.

We are able to report lower rates of postradiosurgery facial weakness and facial numbness with better hearing preservation in this series than in any of our previous series. The incidence of facial weakness developing after radiosurgery was 1.1  $\pm$  0.8% in this series (zero of 101 patients who received  $\leq$  13 Gy compared with two of 89 patients who received  $\geq$  14 Gy). This compares with a 21% rate of facial neuropathy in the 162 patients we treated during our first 5 years of experience (median dose 16 Gy).<sup>11</sup> Facial numbness developed in 2.6  $\pm$  1.2% of patients in the present series compared with 27% of the 162

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treated with higher doses of radiation during our first 5 years.<sup>11</sup> The rate of hearing preservation (same or better Gardner–Robertson class) improved from 51% during our first 5 years to 71.64.7% in the current series. The lower rates of facial weakness, facial numbness, and hearing loss that developed postradiosurgery in the present series compared with previous studies, in which higher-dose radiosurgery was performed, suggest that lowering dose prescriptions for radiosurgery of acoustic neuroma results in fewer complications. It appears that we have already lowered doses below the threshold for causing facial weakness, because no cases developed among the 163 patients who received marginal doses lower than 15 Gy.

Our multivariate analyses of facial, trigeminal, and auditory neuropathies in earlier series of patients with acoustic neuroma who underwent radiosurgery correlated these complications with transverse tumor diameter, which corresponds to the length of nerve irradiated.<sup>4,5,12</sup> In this series we found that hearing loss again correlated with marginal tumor dose, facial weakness correlated slightly better with maximum dose than marginal tumor dose, and trigeminal neuropathy did not significantly correlate with any of the factors studied. The lack of correlation with tumor diameter (nerve length) in this series might mean that tumor diameter is not important when using lower marginal doses or that a small effect is present, but complication rates have dropped so much with lower doses that there are not enough events to detect it. Because only two patients experienced facial weakness, there were not enough events to determine reliably whether maximum dose or marginal dose correlated better with this complication. Another explanation for the association of increases in cranial neuropathy with increases in tumor size observed in the earlier series was that the radiosurgery plans were less conformal for larger tumors and resulted in adjacent cranial nerves receiving higher doses.

In this series we found lower rates of hearing loss, facial numbness, and facial weakness (with no facial neuropathy occurring in patients who received a marginal dose, 15 Gy) with modern procedures and 13-Gy marginal doses without any decrease in tumor control compared with our earlier experience with higher doses. The question remains as to whether marginal doses should be lowered to 12 Gy or less. Although the radiation dose–response curve for control of acoustic neuroma appears flat between marginal doses of 13 to 20 Gy, the tumor-control rate must start to drop at some dose below 13 Gy. Several groups have switched to fractionated stereotactic radiotherapy rather than a reduction in the single-fraction dose as a strategy to reduce complications.<sup>18–20</sup> Hearing loss and facial numbness or weakness may still be a complication of fractionated-dose regimens.<sup>18–20</sup> Comparisons of the two methods would be best accomplished by conducting a randomized trial, but this would be a difficult undertaking. The single-fraction equivalent for a dose of 20 Gy in five fractions<sup>18</sup> would be either 8.9, 9.2, or 11.1 Gy, according to the linear quadratic formula using  $a/b$  ratios of 0, 2.5, or 5, respectively.<sup>3</sup> The  $a/b$  ratio is a radiobiological parameter that represents the ratio of single-hit cell killing ( $a$ ) to cell killing with double-hit kinetics ( $b$ ) for different tissues or tumors. A high  $a/b$  ratio (such as those observed for many early-reacting tissues such as skin or malignant tumors in cell culture) indicates only a small  $b$ , or double-

TABLE 1

*Results of stepwise multivariate proportional hazards analyses of the postradiosurgery development of neuropathies in 190 patients\**

Variable	Facial Neuropathy	Trigeminal Neuropathy	Auditory Neuropathy	
			GR Drop	Deaf
marginal dose	0.0342†	0.7488	0.2995	0.0122†
transverse tumor diameter	0.4584	0.6457	0.0846	0.7789
predicted risk	0.7217	0.8040	0.0748	0.6920
treatment isodose	0.7346	0.7140	0.9691	0.4111
treatment volume	0.9892	0.9218	0.1787	0.6334
age of cobalt sources	0.8761	0.8209	0.5795	0.6459

\*Probability values for each variable are listed. Loss of hearing level preservation was defined as any drop in the Gardner–Robertson hearing level classification (GR Drop) or loss of testable speech discrimination (Deaf). Predicted risks were calculated from risk-prediction formulas derived from a previously reported series of patients who were treated with higher doses, primarily with the aid of computerized tomography scanning (see Flickinger, et al.<sup>4</sup>).

†Statistically significant ( $p < 0.05$ ).

hit, component to cell killing, which is little affected by changing to lower dose fractions. In comparison, late-reacting tissues or tumors with low  $a/b$  ratios (such as central nervous system tissue) are relatively spared when lower-dose fractions are used. An  $a/b$  ratio of zero would correspond to the exponential Neuret formula.<sup>3</sup> The single-fraction equivalent doses for 45 Gy in 25 fractions would be 9, 12.7, or 15.2 Gy for  $a/b$  ratios of 0, 2.5, or 5, respectively. If acoustic neuromas behave as late-reacting tissues, similar to normal brain tissue or cancerous prostate, they should have an  $a/b$  ratio of 2.5 or less.<sup>1</sup> This means that, if fractionated radiotherapy to 20 Gy in five fractions<sup>18</sup> maintains long-term tumor control similar to that achieved in this series, single-fraction radiosurgery doses could theoretically be reduced to a level as low as 9 Gy, with no decrease in tumor control. Theoretically, lowering the marginal dose to 12 Gy or 11 Gy will reduce the rates (projected from present data) of developing decreased hearing levels to 15% or 10%, respectively, and those of new facial numbness to 2.6% or 1.8%, respectively. However, such a strategy would take years to assess any possible reduction in overall tumor-growth control at these dose levels. Current results provide outcomes superior to the other dominant contemporary management option (surgical removal). It is unclear how much, if any, radiosurgical dose prescriptions should be lowered in different patient groups with acoustic neuroma. We are more reluctant to perform radiosurgery with lower marginal doses in patients with acoustic neuromas that have recurred after an apparently complete resection, because these tumors may be more aggressive and patients usually have no remaining hearing to preserve in that ear. Lower-dose radiosurgery may be a better management strategy for patients with bilateral acoustic neuromas (neurofibromatosis Type 2) or patients with contralateral deafness from other causes, in whom hearing preservation may be more important.

## Conclusions

Acoustic neuroma radiosurgery, when performed using

the procedures in place since 1992, is associated with a high rate of tumor-growth control, high rates of hearing preservation, and minimal risks of causing facial and trigeminal morbidity.

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#### References

1. Brenner DJ, Hall EJ: Fractionation and protraction for radiotherapy of prostate carcinoma. **Int J Radiat Oncol Biol Phys** **43**:1095–1101, 1999
2. Cox DR: Regression models and life tables. **J R Stat Soc (B)** **34**:187–202, 1972
3. Flickinger JC, Kalend A: Use of normalized total dose to represent the biological effect of fractionated radiotherapy. **Radiother Oncol** **17**:339–347, 1990
4. Flickinger JC, Kondziolka D, Lunsford LD: Dose and diameter relationships for facial, trigeminal, and acoustic neuropathies following acoustic neuroma radiosurgery. **Radiother Oncol** **41**:215–219, 1996
5. Flickinger JC, Kondziolka D, Pollock BE, et al: Evolution of technique for vestibular schwannoma radiosurgery and effect on outcome. **Int J Radiat Oncol Biol Phys** **36**:275–280, 1996
6. Foote RL, Coffey RJ, Swanson JW, et al: Stereotactic radiosurgery using the gamma knife for acoustic neuromas. **Int J Radiat Oncol Biol Phys** **32**:1153–1160, 1995
7. Gardner G, Robertson JH: Hearing preservation in unilateral acoustic neuroma surgery. **Ann Otol Rhinol Laryngol** **97**:55–66, 1988
8. House JW, Brackmann DE: Facial nerve grading system. **Otolaryngol Head Neck Surg** **93**:146–147, 1985
9. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. **J Am Stat Assoc** **53**:457–481, 1958
10. Kondziolka D, Dempsey PK, Lunsford LD, et al: A comparison between magnetic resonance imaging and computed tomography for stereotactic coordinate determination. **Neurosurgery** **30**:402–407, 1992
11. Kondziolka D, Lunsford LD, McLaughlin MR, et al: Long-term outcomes after radiosurgery for acoustic neuromas. **N Engl J Med** **339**:1426–1433, 1998
12. Linskey ME, Flickinger JC, Lunsford LD: Cranial nerve length predicts the risk of delayed facial and trigeminal neuropathies after acoustic tumor stereotactic radiosurgery. **Int J Radiat Oncol Biol Phys** **15**:227–234, 1993
13. Linskey ME, Lunsford LD, Flickinger JC: Stereotactic radiosurgery for acoustic neurinomas: early experience. **Neurosurgery** **26**:736–745, 1990
14. Mendenhall WM, Friedman WA, Bova FJ: Linear accelerator-based stereotactic radiosurgery for acoustic schwannomas. **Int J Radiat Oncol Biol Phys** **28**:803–810, 1994
15. Noren G, Greitz D, Hirsch A, et al: Gamma knife surgery in acoustic tumours. **Acta Neurochir Suppl** **58**:104–107, 1993
16. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. **Br J Cancer** **35**:1–39, 1977
17. Pollock BE, Lunsford LD, Kondziolka D, et al: Outcome analysis of acoustic neuroma management: a comparison of microsurgery and stereotactic radiosurgery. **Neurosurgery** **36**:215–225, 1995
18. Rashid H, Lowry J, Wertheim S, et al: Improved results for acoustic neuroma (AN) treated with fractionated stereotactic radiosurgery (FSR). **Int J Radiat Oncol Biol Phys** **42**:211, 1998
19. Shirato H, Sakamoto T, Sawamura Y, et al: Comparison between observation policy and fractionated stereotactic radiotherapy (SRT) as an initial management for vestibular schwannoma. **Int J Radiat Oncol Biol Phys** **44**:545–550, 1999
20. Varlotto JM, Shrieve DC, Alexander E III, et al: Fractionated stereotactic radiotherapy for the treatment of acoustic neuromas: preliminary results. **Int J Radiat Oncol Biol Phys** **36**:141–145, 1996

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