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CLINICAL INVESTIGATION **Brain**

LONG-TERM FOLLOW-UP OF ACOUSTIC SCHWANNOMA RADIOSURGERY WITH MARGINAL TUMOR DOSES OF 12 TO 13 Gy

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Purpose: To define long-term tumor control and clinical outcomes of radiosurgery with marginal tumor doses of 12 to 13 Gy for unilateral acoustic schwannoma.

Methods and Materials: A total of 216 patients with previously untreated unilateral acoustic schwannoma underwent Gamma Knife radiosurgery between 1992 and 2000 with marginal tumor doses of 12 to 13 Gy (median, 13 Gy). Median follow-up was 5.7 years (maximum, 12 years; 41 patients with >8 years). Treatment volumes were 0.08–37.5 cm^3 (median, 1.3 cm^3).

Results: The 10-year actuarial resection-free control rate was 98.3% ± 1.0%. Three patients required tumor resection: 2 for tumor growth and 1 partial resection for an enlarging adjacent subarachnoid cyst. Among 121 hearing patients with >3 years of follow-up, crude hearing preservation rates were 71% for keeping the same Gardner-Robertson hearing level, 74% for serviceable hearing, and 95% for any testable hearing. For 25 of these patients with intracanalicular tumors, the respective rates for preserving the same Gardner-Robertson level, serviceable hearing, and testable hearing were 80%, 88%, and 96%. Ten-year actuarial rates for preserving the same Gardner-Robertson hearing levels, serviceable hearing, any testable hearing, and unchanged facial and trigeminal nerve function were 44.0% ± 11.7%, 44.5% ± 10.5%, 85.3% ± 6.2%, 100%, and 94.9% ± 1.8%, respectively.

Conclusions: Acoustic schwannoma radiosurgery with 12 to 13 Gy provides high rates of long-term tumor control and cranial nerve preservation after long-term follow-up. **© 2007 Elsevier Inc.**

Radiosurgery, Stereotactic, Acoustic neuroma, Vestibular schwannoma, Radiation complications.

INTRODUCTION

Radiosurgery is presently a well-established alternative to microsurgical resection of acoustic neuroma (vestibular schwannoma) (1). Many patients prefer radiosurgery to surgical resection because of the lower morbidity of the procedure and similar rates of long-term tumor control (1–4). Although lower than with microsurgery, we reported significant rates of subsequent facial weakness (21%), facial numbness (27%), and decreased hearing (49%) in our first 5 years of experience with acoustic neuroma radiosurgery using marginal tumor doses on the order of 16 Gy (1). Since that time, we reduced marginal tumor dose prescriptions to reduce complications. Treatment techniques have also improved with the substitution of high-resolution stereotactic magnetic resonance imaging over computed tomography (3, 4). In addition, treatment-planning software became more refined, faster, and easier to use. Large numbers of isocenters could be more easily used in plans to achieve greater conformality and sharper dose fall-off (3, 4).

Analysis of our more recent experience over the last decade with improved techniques indicated lower morbidity with similar tumor control compared with our initial experience from 1987 to 1992 (1, 3–5). The use of lower marginal doses has lead to questions of whether high tumor control rates and reduced treatment morbidity will be maintained with longer follow-up. A number of studies looking at outcomes after radiosurgical treatment for acoustic schwannomas have concluded that cranial nerve morbidity related to the procedure will generally manifest itself within 3–5 years of treatment. We recently reported our summary of experience in 829 cases of acoustic schwannomas treated between 1987 and 2002, whereby our experience with treatment-related cranial nerve morbidity was generally seen within 5 years after radiosurgery (6). This article seeks to better define the long-term outcomes with stereotactic radiosurgery as primary treatment of acoustic neuroma using clinically relevant techniques and dosing.

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METHODS AND MATERIALS

Between May 1992 and June 2000, 216 consecutive patients with previously untreated unilateral acoustic neuromas (vestibular schwannomas) underwent Gamma Knife radiosurgery at the University of Pittsburgh with doses of 12 to 13 Gy. The median follow-up was 68 months (maximum follow-up, 143 months). Forty-one patients had follow-up >96 months. Follow-up magnetic resonance scans were normally obtained every 6 months for the first 2 years after radiosurgery, and then yearly thereafter. The median patient age was 56.5 years (range, 22–88 years). One hundred sixteen patients were male and 100 were female. Audiogram results were evaluated according to the Gardner-Robertson classification (7). Serviceable hearing (useful hearing) was defined as Gardner-Robertson (GR) Class 1–2 (speech discrimination >50% and pure tone average <50 dB). Before radiosurgery, 106 patients had GR Class 1–2 hearing (useful or serviceable hearing), 57 patients had Class 3–4 hearing, and 38 patients had no discernible speech discrimination (Class 5). Eighteen patients (8.3%) had trigeminal nerve symptoms (facial numbness, paresthesia, or pain) before radiosurgery.

Radiosurgery was performed with the Model B, C, or U Leksell Gamma Knife (Elekta, Atlanta GA). We used stereotactic magnetic resonance imaging for target definition in all cases. Marginal tumor doses were 12 Gy (n = 21), 12.5 Gy (n = 11), or 13 Gy (median dose, n = 184). Maximum dose varied from 20 to 26 Gy (median, 26 Gy). The marginal tumor dose was prescribed to the 50% isodose volume in 199 patients, 55% in 12, 60% in 4, and 65% in 1 patient. The number of isocenters treated per patient varied from 1 to 16 (median, 6 isocenters). Tumor volume varied from 0.08 to 37.5 cm^3 (median, 1.3 cm^3).

Tumor control was assessed in two ways. Radiographic tumor progression was strictly defined as any temporary or sustained increase in tumor diameter of at least 1 mm in two dimensions or 2 mm in any direction. Because most patients with tumors that increase in size slightly after radiosurgery either stabilize or regress afterward, the primary endpoint for assessing tumor control was freedom from surgical resection (3, 4). Trigeminal neuropathy (facial numbness) was defined as any temporary or permanent, subjective or objective decrease in facial sensation documented either by patient interview or physical examination. Facial neuropathy (facial weakness) was defined as any decrease in facial nerve function as documented by a decrease in House-Brackmann grade (8). We assessed hearing preservation with follow-up audiograms using endpoints of preservation of Gardner-Robertson hearing class (7), preservation of serviceable or useful hearing, and preservation of any testable hearing. Patients without testable speech discrimination at the time of radiosurgery (n = 38) were excluded from any analysis of hearing preservation.

The product limit method of Kaplan and Meier was used to calculate actuarial rates of tumor control and freedom from cranial neuropathies for evaluable patients (9). We performed univariate and stepwise (forward conditional) multivariate analysis using the Cox proportional hazards model with all treatment parameters included as continuous variables (10).

All patients gave informed consent to participate in this retrospective study, which was approved by the University of Pittsburgh institutional review board. All chart reviews and data analyses were conducted before October 1, 2005. All patient identifiers were removed before data analysis.

RESULTS

Tumor control

Three patients required tumor resection: 2 had a complete resection for solid tumor growth and 1 had a partial resection for enlargement of an adjacent subarachnoid cyst. The actuarial 10-year clinical tumor control rate (freedom from surgical resection) for the entire series was 98.3% ± 1.0% (Fig. 1). Temporary or permanent tumor diameter increases of 1 to 2 mm were identified in 7 patients, with 3 shrinking after further follow-up. Counting even temporary 1-mm size increases as failures, the 10-year actuarial imaging-defined tumor control rate was 90.8% ± 3.1%.

Facial neuropathy

No patient in this series developed new facial neuropathy (defined as a temporary or permanent decline in House-Brackmann facial nerve grade) after radiosurgery. Three patients experienced transient episodes of facial twitching on the side of tumor after radiosurgery. One patient was thought to have developed a slight facial palsy on follow-up; however, review of a preoperative interview tape demonstrated the same deficit, thus we did not attribute this to his radiosurgical treatment.

Trigeminal neuropathy

Trigeminal neuropathy (defined as any temporary or permanent subjective decrease in sensation or new pain within the ipsilateral trigeminal nerve distribution after radiosurgery) developed in 8 patients, 5–48 months after radiosurgery. At 10 years, 94.9% ± 1.8% of patients were free of any new trigeminal nerve problems (Fig. 2). Of these 8 patients, 3 developed only transient numbness; another 2 of these patients developed new typical trigeminal neuralgia (10-year actuarial rate, 4.2% ± 1.6% for the entire series). Another patient with perioral numbness had image-defined tumor progression and underwent resection at 36 months with resolution of symptoms. Three patients reported occasional facial pain that was well controlled with medication.

Two patients had symptoms of typical trigeminal neuralgia before radiosurgery. One patient reported decreased pain at last follow-up after undergoing a glycerol rhizotomy procedure at 12 months. The other patient had no pain relief despite slight tumor shrinkage after 34 months. He then underwent repeat radiosurgery to the proximal trigeminal nerve to a maximum dose of 70 Gy at 40 months without relief. Two patients with trigeminal paresthesias before radiosurgery reported reduction in these symptoms afterward.

Hearing preservation

Hearing preservation after radiosurgery was classified in three different ways. Hearing levels (Gardner-Robertson hearing class) were preserved in 100 of 163 evaluable patients (with GR Class 1–4 preoperative hearing before radiosurgery and follow-up audiograms), for a 10-year Gardner-Robertson hearing level preservation-rate of 44.0% ± 11.7% (Fig. 3). Serviceable or useful hearing (GR Class

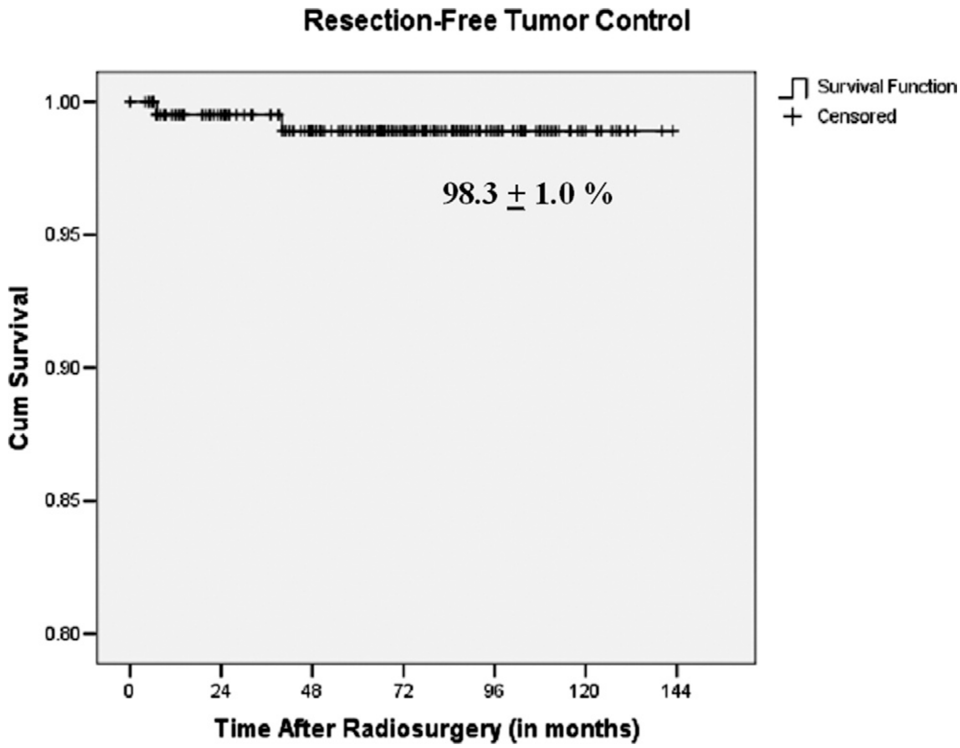

Fig. 1. Actuarial plot of resection-free tumor control in 216 previously untreated unilateral acoustic schwannoma patients after Gamma Knife radiosurgery with marginal tumor doses of 12 to 13 Gy.

1–2) was preserved in 60 of 106 evaluable patients (56.6%), for a 10-year actuarial preservation rate of 44.5% ± 10.5%. In both actuarial curves, there continued to be a fall-off in hearing preservation rates beyond 6 years. A total of 45 events occurred with respect to loss of serviceable hearing, and a total of 54 events were cumulatively seen among

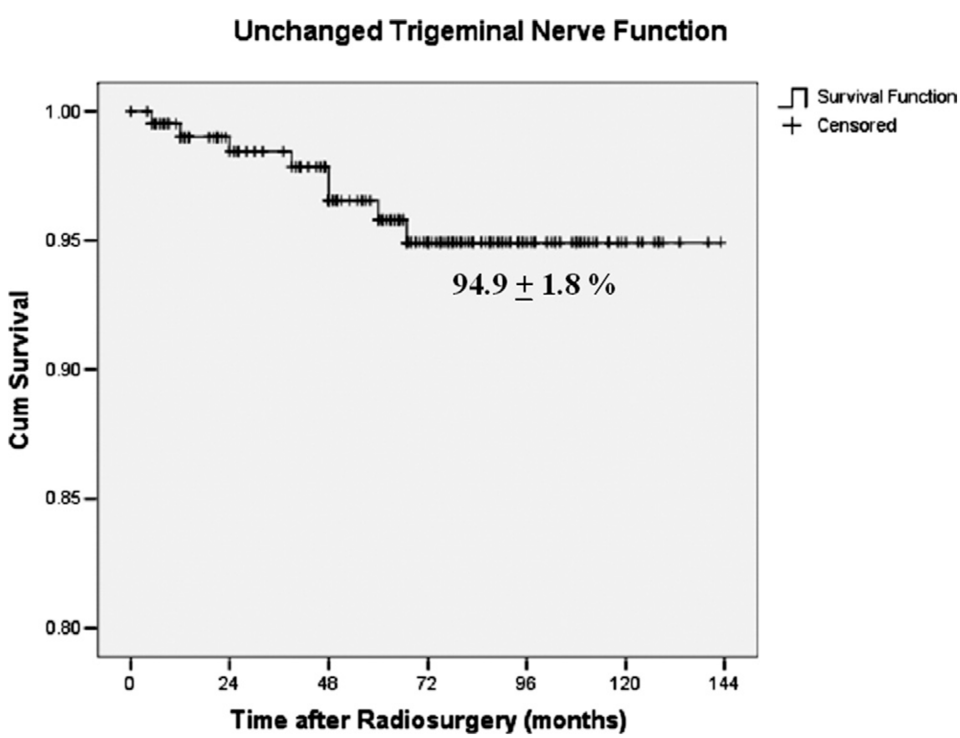

Fig. 2. Actuarial plot of freedom from new trigeminal neuropathy in 216 previously untreated unilateral acoustic schwannoma patients after Gamma Knife radiosurgery with marginal tumor doses of 12 to 13 Gy.

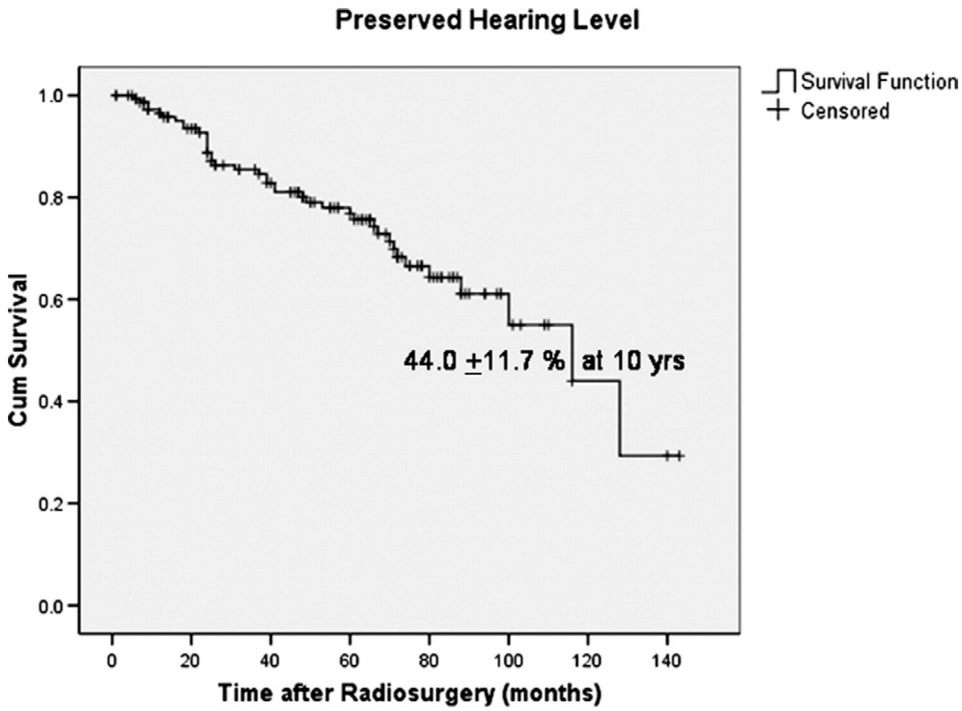

Fig. 3. Actuarial plot for preservation of the same Gardner-Robertson hearing level in 163 evaluable, previously untreated, unilateral acoustic schwannoma patients (with Class 1–4 preoperative hearing) after Gamma Knife radiosurgery with marginal tumor doses of 12 to 13 Gy.

patients who suffered any change in their Gardner-Robertson level of hearing. Events involving loss of useful hearing were seen up to 100 months after radiosurgery. A drop from GR Class 1 to Class 2 hearing level was seen in 2 patients beyond this timeframe (at 116 and 128 months after radiosurgery). Hearing improved by 1 class, 4 to 24 months after radiosurgery, in 5 patients. In 1 of these patients, hearing was eventually lost on later follow-up. One patient improved in hearing from GR Class 3 to Class 1 at 19 months. Two patients who maintained GR Class 1 serviceable hearing noted a subjective improvement in speech discrimination after treatment. Preservation of any testable hearing by pure tone audiometry (at least able to hear a loud noise in the affected ear) was accomplished in 162 of 169 evaluable patients, for a 10-year actuarial preservation rate for any testable hearing of 85.3% ± 6.2% (Fig. 4).

Among 110 patients with testable hearing and >3 years' follow-up, crude hearing preservation rates were 78% for keeping the exact same Gardner-Robertson hearing level (1–4), 77% for serviceable hearing (starting with GR Class 1 or 2 hearing and preserving at least level 2), and 97% for preserving any testable level of hearing (at least able to hear a loud noise in the affected ear). Of these patients, the 25 with intracanalicular tumors had crude hearing preservation rates of 80% for preservation of the same Gardner-Robertson hearing level, 88% for preservation of serviceable hearing, and 96% preserved some level of testable hearing (able to at least hear loud noise in the affected ear).

Multivariate analysis

Univariate and multivariate analyses of the effects of radiosurgery on cranial nerve VIII (any decrease in Gardner-Robertson hearing level and/or loss of serviceable hearing) were performed using the Cox proportional hazards model. The treatment variables tested were marginal dose (the minimum tumor dose), the maximum dose, treatment volume, transverse tumor diameter, and patient age. Table 1 summarizes the results of multivariate analyses of the development of postradiosurgery auditory neuropathy. As shown in Table 1, treatment volume was the only variable tested that significantly correlated with drop in hearing level ($p = 0.023$). Treatment volume did not significantly correlate with preservation of serviceable hearing (GR Class 1 to Class 2). The low number of trigeminal events in this series precluded us from conducting a reliable multivariate analysis of that endpoint.

DISCUSSION

Our long-term evaluation of tumor control using marginal doses of 12 to 13 Gy with modern radiosurgery techniques in this series was favorable. The actuarial 10-year clinical tumor control rate (no requirement for surgical intervention) for this current series was 98.3% ± 1.0%. This compares to a long-term resection-free clinical tumor control rate of 98% among the patients treated to higher doses (median dose, 16 Gy) in our first 5 years of experience (1). It also compares favorably to other series using radiosurgery, fractionated

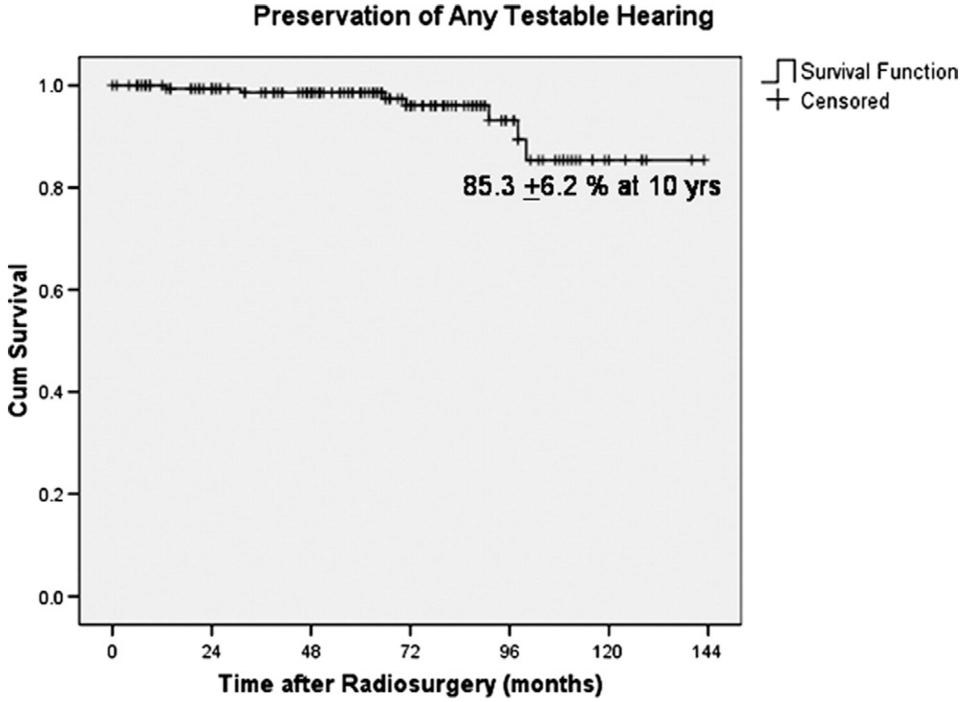

Fig. 4. Actuarial plot for preservation of any testable hearing level in 169 evaluable, previously untreated, unilateral acoustic schwannoma patients (with Class 1–4 preoperative hearing) after Gamma Knife radiosurgery with marginal tumor doses of 12 to 13 Gy.

radiotherapy, or microsurgical resection to manage acoustic neuroma (11–23). Although most patients in this series showed some evidence of recent progression of symptoms or increase in tumor size, these were not used as absolute selection criteria for treatment in this series. We did not record how many patient seemed to have "quiescent" tumors at the time of radiosurgery in this study. It is possible that comparisons of short-term tumor control rates could be biased between centers that observe all acoustic tumors before treating after undisputed tumor progression and other centers that are more liberal in their selection criteria. Because of the natural tendency for all acoustic schwannomas to eventually grow, it should make less of a difference with longer follow-up.

We found acceptable rates for preservation of facial and trigeminal nerve function in this series. Facial nerve preservation was 100%. Normal trigeminal nerve function was preserved in 94.9% of patients. The rates of facial and trigeminal nerve dysfunction were in line with our experience from 1992 to 1997, as well as our initial series of patients treated with marginal doses of 12 to 13 Gy. We found in our earlier experience with higher marginal doses that all of the cranial neuropathies seemed to occur within 2, or at most 3 years after radiosurgery. Regarding hearing preservation, we were surprised to discover continued hearing loss beyond 5 years of follow-up. Although we found 6-year actuarial rates that were somewhat similar to the overall preservation rates of Gardner-Robertson and useful hearing, the 10-year rates had lessened. In this series, tumor control continues to remains high with long-term follow up, whereas hearing loss and trigeminal nerve dysfunction (for larger tumors that indent the trigeminal root) continue to occur. Certainly, careful exploration of lower marginal doses seems reasonable in trying to reduce cranial nerve complications. On the basis of the data from this series, it is possible that even with the use of lower marginal doses, hearing preservation may continue to suffer in the long term.

Chang *et al.* (24) recently reported on treatment outcomes of 61 patients treated with Cyber Knife radiosurgery with more than 36 months of follow-up. They reported an imaging-defined tumor control rate of 98%. Useful hearing preservation was possible in 74% of their patients, which they reported as a crude rate as opposed to a 10-year actuarial rate. Our crude rate of useful hearing preservation in patients with more than 3 years of follow-up was similar at 74%. Chang *et al.* found no evidence of permanent facial or

Table 1. Cox multivariate analyses of postradiosurgery preservation of the same Gardner-Robertson (GR) hearing class (1–4 only) and preservation of serviceable (GR Class 1–2) hearing

Variable	*p* (preserved GR)	*p* (serviceable)
Age	0.939	0.884
Treatment volume	0.023*	0.472
Transverse tumor diameter	0.753	0.757
Marginal dose	0.544	0.472
Maximum dose	0.470	0.879

* Indicates statistical significance.

trigeminal neuropathy (24). Large long-term studies examining the efficacy of this modality of radiosurgery with respect to tumor control rates and cranial nerve preservation are needed.

There have been a number of recent studies examining long-term outcomes in patients treated with Gamma Knife radiosurgery or fractionated stereotactic radiotherapy (FSRT) (25–28). With respect to FSRT, Combs *et al.* (25) recently reported results of 106 patients treated at their institution. Using a median dose of 57.6 Gy given in 1.8 Gy per day, they treated 106 patients with a median follow-up period of 48.5 months. Actuarial tumor control rates from that study were 94.3% and 93% at 3 and 5 years, respectively. They reported "actual" hearing rate preservation of 94% at 5 years. This was ascertained through telephone follow-up and questionnaires rather than audiograms in the majority of patients. They reported facial and trigeminal nerve damage in 3.4% and 2.8% of patients, respectively. They concluded that FSRT allowed for a lower incidence of late morbidity, including facial palsy, trigeminal nerve palsy, or hearing loss due to the beneficial effect of fractionation compared with single fraction radiosurgery, while maintaining high rates of tumor control. This is in contrast to a comparison of observation vs. FSRT in 77 patients performed by Shirato *et al.* (15). After a mean follow-up period of 35 months in the observation group and 31 months in the FSRT group, they were able to find a statistically significant improvement in tumor control in the latter but no difference in the Gardner-Robertson class preservation curves for 5 years after initial presentation.

A recent study reported by Hasegawa *et al.* (28) looked at 317 patients treated with Gamma Knife stereotactic radiosurgery with a minimum follow-up period of 5 years and a median follow-up period of 7.8 years. They reported 5- and 10-year progression-free survival rates of 93% and 92%, respectively. In subgroup analysis of patients treated with 13 Gy or less, they found a hearing preservation rate of 68%, facial numbness in 2%, and a 10-year progression-free survival rate of 94%. With respect to their hearing preservation data, the median follow-up was not noted in the study. Their long-term findings with respect to tumor control concur with the data we have presented here.

This series provides a relatively long follow-up of patients treated with clinically relevant marginal tumor doses, with 41 patients followed for more than 8 years and 11 patients followed for more than 10 years. It is generally accepted that almost all cases of postradiosurgery facial, trigeminal, and auditory neuropathy occur within the first 3 years after treatment, and this would seem to bear out with our current analysis, except for continued hearing loss in this series of patients beyond 5 years. We hypothesize that with lower marginal doses and longer follow-up hearing loss may continue through a number of mechanisms, including direct radiation effects, vascular effects, and changes in the tumor remnant. It would be interesting to compare these hearing preservation rates with those seen in patients who have undergone observation or fractionated radiotherapy with audiometric follow-up for more than 5 years.

Acoustic neuroma radiosurgery with marginal doses of 12 to 13 Gy is associated with a high rate of tumor control with minimal facial and trigeminal morbidity. These observations remain durable in long-term follow-up for most patients.

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