Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 November 1; 81(3): 647–653. doi:10.1016/j.ijrobp.2010.06.006.

LONG-TERM OUTCOMES OF VESTIBULAR SCHWANNOMAS TREATED WITH FRACTIONATED STEREOTACTIC RADIOTHERAPY: AN INSTITUTIONAL EXPERIENCE

SUMIT KAPOOR, M.B.B.S., M.P.H.^{*}, SACHIN BATRA, M.B.B.S., M.P.H.^{*}, KATHRYN CARSON, SC.M.[†], JOHN SHUCK, B.A.^{*}, SIDDHARTH KHARKAR, M.B.B.S., M.H.S.^{*}, RAHUL GANDHI^{*}, JUAN JACKSON, C.M.D.[‡], JAN WEMMER, C.R.N.P.[‡], STEPHANIE TEREZAKIS, M.D.[‡], ORI SHOKEK, M.D.[‡], LAWRENCE KLEINBERG, M.D.[‡], and DANIELE RIGAMONTI, M.D.^{*}

^{*}Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MD

[‡]Department of Radiation Oncology, Johns Hopkins Hospital, Baltimore, MD

[†]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

Purpose—We assessed clinical outcome and long-term tumor control after fractionated stereotactic radiotherapy (FSRT) for unilateral schwannoma.

Methods and Materials—Between 1995 and 2007, 496 patients were treated with fractionated stereotactic radio-therapy at Johns Hopkins Hospital (Baltimore, MD); 385 patients had radiologic follow-up that met the inclusion criteria. The primary endpoint was treatment failure. Secondary endpoints were radiologic progression and clinical outcome. Logistic regression analysis assessed the association of age, race, tumor side, sex, and pretreatment symptoms.

Results—In 11 patients (3%) treatment failed, and they required salvage (microsurgical) treatment. Radiologic progression was observed in 116 patients (30.0%), including 35 patients (9%) in whom the treatment volume more than doubled during the follow-up period, although none required surgical resection. Tumors with baseline volumes of less than 1 cm³ were 18.02 times more likely to progress than those with tumor volumes of 1 cm³ or greater (odds ratio, 18.02; 95% confidence interval, 4.25–76.32). Treatment-induced neurologic morbidity included 8 patients (1.6%) with new facial weakness, 12 patients (2.8%) with new trigeminal paresthesias, 4 patients (0.9%) with hydrocephalus (1 communicating and 3 obstructive), and 2 patients (0.5%) with possibly radiation-induced neoplasia.

Conclusions—Although the rate of treatment failure is low (3%), careful follow-up shows that radiologic progression occurs frequently. When reporting outcome, the “no salvage surgery

needed” and “no additional treatment needed” criteria for treatment success need to be complemented by the radiologic data.

Keywords

Vestibular schwannoma; Fractionated stereotactic radiotherapy; Tumor progression; Clinical outcomes

INTRODUCTION

The vestibular schwannoma (VS) is a benign tumor arising from the Schwann cells of the vestibulocochlear nerve. The overall incidence of VS is about 1 per 100,000 person-years, and it appears to be increasing (1, 2). The prevalence of incidental VS is reported to be between 2 and 7 in 10,000 people (3, 4), implying that the numbers of asymptomatic VS may be larger than previously suspected. Patients with VSs most commonly present with unilateral hearing problems, hearing loss, or tinnitus, which is usually progressive. Other less common symptoms are vertigo, gait imbalance, facial numbness, and facial tingling.

Magnetic resonance imaging (MRI), enabling detection of tumors as small as 1 to 2 mm in diameter, has made possible earlier diagnosis (5) and easy follow-up of these tumors. Measurements from MRI scans can reliably detect changes as small as 1.1 mm in tumor diameter and 0.15 cm³ in tumor volume (6).

Surgical resection has been the preferred treatment modality for the past 50 years, but now many centers offer radiation (4) as the first treatment. The rationale for this choice is that total removal is not always feasible without significant morbidity (7), whereas radiation aimed at arresting tumor growth seems to be associated with fewer complications (8, 9).

Tumors selected for treatment with radiation can be treated either with fractionated stereotactic radiotherapy (FSRT) or with single-treatment radiosurgery. Both of these techniques are known to be highly efficacious, with most studies estimating a tumor control rate above 95% (10–12). We report tumor control of unilateral tumors with FSRT.

METHODS AND MATERIALS

From November 1995 until November 2007, 516 patients with unilateral VS were treated at Johns Hopkins Hospital (Baltimore, MD). The majority of the patients in this series underwent treatment shortly after the diagnosis was made. In the last 3 years, a period of observation was required, and treatment was offered only if follow-up MRI showed unequivocal growth. The patients were prospectively followed up after treatment after their clinical and radiosurgical status, including tridimensional measurements and the calculation of the tumor size, was recorded. We excluded 20 patients (3.9%) treated with Gamma Knife from our study, and 496 patients (96.1%) treated with FSRT were included. After approval by the Johns Hopkins Medical Institutions Institutional Review Board with a waiver of informed consent, data from medical records were retrospectively reviewed. Abstracted data included demographic characteristics, pretreatment symptoms, post-treatment complications, and tumor volume at each visit preceding and after treatment.

Tumor volume

Tumor volume was calculated by use of the treatment software at the time of the radiosurgical procedure, and that at follow-up was estimated from axial and coronal T1-weighted MRI scans taken after injection of gadolinium contrast by dividing the product of the three largest perpendicular dimensions of the tumor (*i.e.*, anterior–posterior, transverse, and craniocaudal) by 2. The estimates of VS volume by use of this ellipsoid method on conventional gadolinium-enhanced MRI have been shown to strongly correlate with volumes obtained by the voxel count method in high-resolution constructive interference in steady state imaging ($r = 0.98$, $p = 0.001$) (13). Tumor volumes were measured at the time of treatment (baseline) and at 6-month intervals for 2 years after treatment and yearly thereafter. Patients were only included for analysis if they had at least 18 months' follow-up, because "enlargement," "tumor expansion," and "transient expansion" (14) have commonly resolved by this time.

There is no agreement in the literature on the definition of "tumor control"; some authors define it as local control after radiation treatment, implying stabilization of tumor growth or regression with no evidence of progression on follow-up evaluations (8), whereas most define it as "no additional treatment needed" or "no salvage surgery required" (11, 12, 15). Unfortunately, these different definitions of the endpoint make it problematic to compare the efficacy of this procedure across studies.

To more precisely determine treatment outcome, we used an operational definition based on clinical and radiologic criteria: (1) Therapeutic success was defined as tumor volume at last follow-up less than or equal to the pretreatment volume and the patient having a stable clinical status. (2) Therapeutic failure was defined as progressive tumor growth with associated symptoms, requiring surgical resection. (3) Radiologic progression was defined as tumor volume greater than the baseline volume and a stable clinical status at follow-up. Radiologic progression was considered significant when the tumor volume at last follow-up was more than double the treatment volume.

Treatment planning

All patients were treated with highly conformal radiation, generally by use of Brain Scan software, version 5.3, on a Brainlab Treatment Planning System (Brainlab, Munich Germany). Fractionated stereotactic Fractionated Stereotactic Radiosurgery consisted of either 5 fractions of 5 Gy each or 10 fractions of 3 Gy each. Doses were specified to the 80% isodose line to completely encompass the tumor volume. Before July 2000, 32 patients received treatment at the 85% or 90% isodose line. Of the patients, 340 (89.47%) received 5 fractions and 36 (9.47%) received 10 fractions of 300 cGy each. The neurosurgeon outlined the gross tumor volume. Until 2002, we did not add margins, and afterward, a 2-mm margin was added to the gross tumor volume to determine the planned tumor volume. This approach was selected based on the good therapeutic ratio previously shown with this dosing regimen with less conformal technologies. The goal was to administer optimal doses of radiation through use of this fractionated regimen and conformal technology to prevent radiation toxicity from unnecessary exposure to surrounding structures and provide high long-term tumor control rates.

Statistical analysis

Demographic and clinical characteristics were summarized and compared by radiologic and treatment outcome status. Categorical data were described with frequencies and percentages, and groups were compared by use of the Fisher exact tests. Continuous measures were summarized by use of means and standard deviations or, if data were highly skewed, medians and ranges, and group comparisons were made by use of two-sample *t* tests or Wilcoxon rank-sum tests. The follow-up time for each patient and outcome was calculated from the date of treatment until the date of the last clinical/MRI visit and the date of surgery for patients needing microsurgery. Failure rates were calculated for patients available for evaluation of tumor volume at intervals of 18 months to 3 years, 3 to 4 years, 4 to 5 years, and after 5 years of follow-up and compared by use of the Fisher exact test. Logistic regression analysis was performed to identify factors associated with significant radiologic progression at last follow-up. Kaplan-Meier analysis was performed to obtain median time to significant progression and to radiologic progression. The progression times were stratified and compared between variables by use of the log-rank test.

Statistical analysis was performed with Stata 9.0 (StataCorp, College Station, TX). Confidence intervals (CIs) were calculated by use of standard methods. All reported *p* values are two sided, and statistical significance was set at *p* < 0.05.

RESULTS

Demographic and clinical characteristics of the 496 patients treated with FSRT are described in Table 1. The patients' mean age was 53.9 years, 52.4% were male, and 87.5% were white. Right-sided tumors were seen in 54.7% of patients.

Of the 496 patients, 71 (14.3%) were lost to follow-up and had no post-treatment volume data. The remaining 425 patients had a median time of follow-up of 52 months (range, 5–138 months). The analysis was limited to 385 patients who had a minimum of 18 months of follow-up. The median follow-up for these 385 patients included in the study was 56 months (range, 18–138 months).

Radiologic outcome of 385 patients with volumetric data

Baseline tumor volumes ranged from 0.01 to 26.30 cm³, with a median of 0.890 cm³ and a mean of 2.660 cm³. We arbitrarily defined small tumors as volume less than 1 cm³ and large tumors as 1 cm³ or greater. Outcome rates are presented in Table 2. Therapeutic and radiologic success was observed in 258 patients (67.0%). Therapeutic failure was observed in 11 patients (3%) requiring surgery because of large size of the tumor causing neurologic symptoms. Radiologic progression at last follow-up was observed in 116 patients (30.0%), including 35 patients (9%) in whom the treatment volume more than doubled during the follow-up period (Table 3). We arbitrarily defined this latter group as having “significant radiologic progression.” Of these 35 tumors, 33 occurred in the 197 patients (16.7%) with small tumors, as compared with only 2 in the 188 patients (1.06%) with large tumors (Table 2). The median time to radiologic progression (116 patients) was 91.68 months (95% CI, 83.95–100.45 months) (Fig 1).

Logistic regression analysis showed that patients with pre-treatment tumor volumes of less than 1 cm³ were almost 18 times more likely to grow to more than double the treatment volume than those with volumes of 1 cm³ or greater (odds ratio [OR], 18.02; 95% CI, 4.25–76.32). This significant progression occurred at a rate of 4% to 5% until 60 months of follow-up and then significantly dropped to 1.5% ($p = 0.01$) (Table 4). When the dose was analyzed, it was not found to be a significant predictor of radiologic control on logistic regression (OR, 0.99; 95% CI, 0.993–1.0004; $p = 0.088$). This may be so because the majority of patients received 25 Gy at the 80% isodose line.

Demographic characteristics and pretreatment symptoms for patients by outcome status are compared in Table 5. The groups did not differ in age or race. However, there was a significant difference between failures and nonfailures with regard to the proportion of female patients, right-sided schwannomas, and pretreatment clinical features such as facial paresthesias, headaches, and gait imbalance (Table 5). Of the 11 patients classified as failures, 10 were women (90.01%), as compared with 46.26% of nonfailures who were women ($p = 0.03$). Headache was more prevalent in patients who had treatment failure (36.36%) as compared with patients who did not require salvage surgery (7.22%) ($p = 0.008$). Facial paresthesia was present in 45.45% of patients among failures, whereas among nonfailures, it occurred in 18.45% of patients ($p = 0.041$). Gait imbalance tended to be more frequent among failures (63.64%) as compared with nonfailures (38.77%) ($p = 0.12$).

Among 35 patients with significant radiologic progression, 33 (94.29%) had a baseline tumor volume smaller than 1 cm³, whereas 162 (47.79%) of the patients who did not have significant failure harbored small tumors. No other pretreatment clinical feature significantly differed between these patients. In bivariate logistic regression, patients with small tumors (volume <1 cm³) were 18 times more likely to fail than patients with larger tumors (OR, 18.02; 95% CI, 4.25–76.32; $p < 0.001$). Although patients with pretreatment tinnitus, ear fullness, gait imbalance, or facial twitching tended to have an association with significant failure, they did not attain statistical significance on bivariate or univariate analysis. The only significant variable on multivariate analysis was the small baseline tumor size (baseline volume <1 cm³).

Clinical outcomes of 496 patients

Facial nerve before and after treatment—Before treatment, 12 patients (2.4%) complained of facial weakness symptoms, and of these, 4 patients (0.8%) had persistence of symptoms after treatment. New facial weakness developed in 8 patients (1.6%) after the treatment.

Trigeminal paresthesia before and after treatment—Before treatment, 86 patients (17.3%) complained of facial paresthesias, and of these, only 9 (1.8%) continued to have the symptoms after treatment. New onset of trigeminal paresthesias occurred in 12 patients (2.8%).

Other complications—Hydrocephalus was observed in 4 patients (0.9%): communicating hydrocephalus in 1 and obstructive hydrocephalus in 3. The communicating hydrocephalus was treated with shunt insertion. Two patients with obstructive

hydrocephalus were treated with resection of schwannoma alone, whereas the third patient required resection and shunt for hydrocephalus. Possibly radiation-induced neoplasia was observed in 2 patients (0.5%).

DISCUSSION

The natural history of VSs is not well known; retrospective studies suggest that 53% continuously grow and 7% to 10% remain stable, whereas up to 30% involute (16). A few prospective series showed that untreated VSs regress in 7% to 20% of cases and remain stable in 40% to 85% (2, 17–21) whereas only 18% to 55% tumors show progression (2, 17–19, 21). Most studies report tumor control of 92% to 100% after radiosurgical treatment. It is intuitive that without confirming tumor growth during a period of observation before the treatment, the possibility exists to treat some stable tumors. Monitoring a tumor over at least 6 to 12 months to confirm tumor growth before treatment aims at eliminating this problem. For this reason, many physicians, including ourselves, are now choosing a period of observation with MRI monitoring to document growth before recommending treatment (17, 18, 22).

There are no current treatment guidelines or recommendations based on patient characteristics or tumor size. In the past few decades, standard treatment for larger tumors was micro-surgical resection (23) or a combination of microsurgery and radiotherapy (4), whereas management of patients with small- to moderate-sized tumors was more controversial (9). However, over the past 10 years, radiation treatment for VS has been increasingly used as an alternative to microsurgery because it is claimed that it results in high rates of control and elimination of the operative morbidity and because early outcomes are better for patients having stereotactic radiotherapy compared with surgical resection (9). Such change in practice is predicated on the assumption that early outcomes remain stable over time (9).

There is, however, no consensus on the description of the response of tumor to radiation, with some radiosurgical series suggesting that these tumors respond similarly regardless of size (24) whereas some show otherwise. For example, Lederman *et al.* (25) reported that 61% of small tumors shrank in size compared with 81% of the larger tumors. This finding seems to corroborate our own observation that small tumors carry a higher risk of treatment failure. Furthermore, Mirz *et al.* (2) report an inverse correlation between tumor size and growth rate of untreated tumors ($r = -0.47$, $p = 0.001$). Similarly, Fucci *et al.* (26) observed higher mean tumor volume of conservatively managed tumors that regressed as compared with those that were stable or growing. Growth occurred in 5 (70%) of the 7 tumors larger than 20 mm; however, this subset comprised only 13.9% of the tumors that grew. Similar to this, Luetje (27) reported spontaneous involution in 6 (12.8%) of the 47 patients who were managed conservatively and showed that tumor volume tended to be higher for tumors that regressed as compared with those that remained stable or grew during the follow-up. The author suggested intravascular thrombosis, ischemic changes, and organization of necrosis by fibrosis in large tumors as possible mechanisms for spontaneous regression. These observations suggest that large tumors not only tend to spontaneously regress or have small growth rates but may also be more amenable to radiotherapy, which induces changes similar

to those described previously. In agreement with this, our study found a very strong association of significant radiologic progression and baseline tumor size, with failure rates being about 18 times higher for patients with tumors of less than 1 cm³ in volume than those with a volume of 1 cm³ or greater.

Another important component in the definition of tumor control is time. Early on, tumors might increase in size because of the effect of radiation, but later, they shrink. Late growth usually signifies failure of treatment. Fuss *et al.* (23) showed that the tumor control rate decreased over time (*i.e.*, 100% and 95% at 2 and 5 years, respectively). Our findings suggest that the majority of the failures will be apparent by the end of the fifth year, after which new failures are less frequent. All these facts show the importance of at least 5 years of follow-up after treatment and the need to be vigilant toward behavior indicating tumor progression.

Tumor control rates reported in linear accelerator (LINAC) series, where the stereotactic irradiation has been given in fractionated mode, irrespective of fractionation schedules (28), are on par with the reported outcome in the largest radio-surgery series using one fraction (Gamma Knife; Elekta AB, Stockholm, Sweden) (11, 12). In our study, however, absolute success both therapeutically and radiologically (*i.e.*, patients whose last tumor volume was either less than or equal to the baseline volume and who did not show any clinical signs of disease progression) was seen in only 67.0% of patients.

Failure—defined as clinical progression due to mass effect from an increase in tumor size due to recurrence or radiation-induced tumor edema, requiring microsurgery—was observed in 11 (3%) of our patients. Five of these patients had an increase in size caused by radiation edema, which was recognized by the presence of heterogeneous non-enhancing regions in the tumor. Some radiologic progression occurred in 30% of patients. A significant radiologic progression, defined as tumor volume at last follow-up more than double the baseline tumor volume, was observed in 9% of patients (35 patients). All these patients have not yet required microsurgery because their tumor volume at baseline was small, and despite the obvious growth, the tumors have not caused clinical deterioration requiring surgery. In addition, we assessed tumor volume to identify progressions instead of less sensitive linear measurements used by most studies (Fig 2). Our policy of selecting patients with growth documented on MRI was applied after mid 2003. The majority of patients did not undergo a period of observation. This means that we may have treated some stable tumors.

When the primary endpoint for tumor control is “no additional treatment needed” or “no salvage surgery needed,” the control rate by use of Gamma Knife is about 98% (11, 12). Unfortunately, these important studies do not provide data regarding tumor volume at follow-up. Because a large percentage of patients in these series harbor small tumors (11, 12), even if treatment clearly failed with definitive radiologic progression to as high as twice the baseline volumes or more, these patients have “no need of salvage surgery or additional treatment” during a limited period of follow-up. This statement is corroborated by data from a small Japanese study, where a group of 52 patients treated with Gamma Knife were followed up for at least 5 years, with only 1 patient (2%) lost to follow-up. Their reported

failure rate is parallel to our experience, wherein the treatment failure rate was 3% and the significant progression rate was 9% (29).

Therefore “no additional treatment needed” and “no salvage surgery needed” are inadequate endpoints to assess treatment success unless an adequate length of follow-up is obtained; furthermore, these should be used with great caution and alongside the concept of radiologic progression when discussing treatment options with the patient.

Our experience supports the statement that radiotherapy is a useful tool in the management armamentarium of VS. However, except for special circumstances, a period of observation of 6 to 12 months before proceeding with treatment is recommended. We believe that long-term and careful follow-up of treated patients with monitoring of tumor volume for more than 5 years is necessary to ascertain the true success rate of radiation treatment.

Acknowledgments

This work was supported by grants from the Salisbury Foundation, the Monica and Hermen Greenberg Foundation, and the Swenson Foundation. These grants supported design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

REFERENCES

1. Propp JM, McCarthy BJ, Davis FG, et al. Descriptive epidemiology of vestibular schwannomas. *Neuro Oncol.* 2006; 8:1–11. [PubMed: 16443943]
2. Mirz F, Pedersen C, Fiirgaard B, Lundorf E. Incidence and growth pattern of vestibular schwannomas in a Danish county, 1977-98. *Acta Otolaryngol Suppl.* 2000; 543:30–33. [PubMed: 10908969]
3. Anderson T, Loevner L, Bigelow D, Mirza N. Prevalence of un-suspected acoustic neuroma found by magnetic resonance imaging. *Otolaryngol Head Neck Surg.* 2000; 122:643–646. [PubMed: 10793339]
4. Lin D, Hegarty JL, Fischbein NJ, et al. The prevalence of “incidental” acoustic neuroma. *Arch Otolaryngol Head Neck Surg.* 2005; 131:241–244. [PubMed: 15781765]
5. Likhterov I, Allbright RM, Selesnick SH. LINAC radiosurgery and radiotherapy treatment of acoustic neuromas. *Otolaryngol Clin North Am.* 2007; 40:541–570. ix. [PubMed: 17544695]
6. Slaterry WH III, Fisher LM, Yoon G, et al. Magnetic resonance imaging scanner reliability for measuring changes in vestibular schwannoma size. *Otol Neurotol.* 2003; 24:666–670. discussion 670–661. [PubMed: 12851562]
7. Maire JP, Huchet A, Milbeo Y, et al. Twenty years’ experience in the treatment of acoustic neuromas with fractionated radio-therapy: A review of 45 cases. *Int J Radiat Oncol Biol Phys.* 2006; 66:170–178. [PubMed: 16904521]
8. Mendenhall WM, Friedman WA, Amdur RJ, et al. Management of acoustic schwannoma. *Am J Otolaryngol.* 2004; 25:38–47. [PubMed: 15011205]
9. Pollock BE, Driscoll CL, Foote RL, et al. Patient outcomes after vestibular schwannoma management: A prospective comparison of microsurgical resection and stereotactic radiosurgery. *Neurosurgery.* 2006; 59:77–85. discussion 77–85. [PubMed: 16823303]
10. Koh ES, Millar BA, Menard C, et al. Fractionated stereotactic radiotherapy for acoustic neuroma: Single-institution experience at The Princess Margaret Hospital. *Cancer.* 2007; 109:1203–1210. [PubMed: 17318817]
11. Chopra R, Kondziolka D, Niranjan A, et al. Long-term follow-up of acoustic schwannoma radiosurgery with marginal tumor doses of 12 to 13 Gy. *Int J Radiat Oncol Biol Phys.* 2007; 68:845–851. [PubMed: 17379451]

12. Regis J, Delsanti C, Roche PH, et al. Functional outcomes of radiosurgical treatment of vestibular schwannomas: 1000 successive cases and review of the literature [in French]. *Neurochirurgie*. 2004; 50:301–311. [PubMed: 15179283]
13. Yamada I, Tsunoda A, Noguchi Y, Komatsuzaki A, Shibuya H. Tumor volume measurements of acoustic neuromas with three-dimensional constructive interference in steady state and conventional spin-echo MR imaging. *J Magn Reson Imaging*. 2000; 12:826–832. [PubMed: 11105020]
14. Nagano O, Higuchi Y, Serizawa T, et al. Transient expansion of vestibular schwannoma following stereotactic radiosurgery. *J Neurosurg*. 2008; 109:811–816. [PubMed: 18976069]
15. Schwaber M. Fractionated Stereotactic Radiation for Acoustic Neuroma. *eMedicine Journal*. 2001; 2
16. Bederson J, von Ammon K, Wichmann W, et al. Conservative treatment of patients with acoustic tumors. *Neurosurgery*. 1991; 28:646–650. discussion 650–641. [PubMed: 1876241]
17. Hajioff D, Raut V, Walsh R, et al. Conservative management of vestibular schwannomas: Third review of a 10-year prospective study. *Clin Otolaryngol*. 2008; 33:255–259. [PubMed: 18559034]
18. Deen H, Ebersold M, Harner S, et al. Conservative management of acoustic neuroma: An outcome study. *Neurosurgery*. 1996; 39:260–264. discussion 264–266. [PubMed: 8832662]
19. Massick D, Welling D, Dodson E, et al. Tumor growth and audiometric change in vestibular schwannomas managed conservatively. *Laryngoscope*. 2000; 110:1843–1849. [PubMed: 11081597]
20. Mohyuddin A, Vokurka EA, Evans DG, et al. Is clinical growth index a reliable predictor of tumour growth in vestibular schwannomas? *Clin Otolaryngol Allied Sci*. 2003; 28:85–90. [PubMed: 12680824]
21. Stipkovits E, Graamans K, Vasbinder G, Van Dijk J, Beek F. Assessment of vestibular schwannoma growth: Application of a new measuring protocol to the results of a longitudinal study. *Ann Otol Rhinol Laryngol*. 2001; 110:326–330. [PubMed: 11307907]
22. Martin T, Tzifa K, Kowalski C, et al. Conservative versus primary surgical treatment of acoustic neuromas: A comparison of rates of facial nerve and hearing preservation. *Clin Otolaryngol*. 2008; 33:228–235. [PubMed: 18559028]
23. Fuss M, Debus J, Lohr F, et al. Conventionally fractionated stereotactic radiotherapy (FSRT) for acoustic neuromas. *Int J Radiat Oncol Biol Phys*. 2000; 48:1381–1387. [PubMed: 11121637]
24. Williams JA. Fractionated stereotactic radiotherapy for acoustic neuromas. *Int J Radiat Oncol Biol Phys*. 2002; 54:500–504. [PubMed: 12243828]
25. Lederman G, Lowry J, Wertheim S, et al. Acoustic neuroma: Potential benefits of fractionated stereotactic. *Stereotact Funct Neurosurg*. 1997; 69:175–182. [PubMed: 9711752]
26. Fucci M, Buchman C, Brackmann D, Berliner K. Acoustic tumor growth: Implications for treatment choices. *Am J Otol*. 1999; 20:495–499. [PubMed: 10431892]
27. Luetje C. Spontaneous involution of acoustic tumors. *Am J Otol*. 2000; 21:393–398. [PubMed: 10821554]
28. Meijer OW, Vandertop WP, Baayen JC, et al. Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: A single-institution study. *Int J Radiat Oncol Biol Phys*. 2003; 56:1390–1396. [PubMed: 12873685]
29. Iwai Y, Yamanaka K, Shiotani M, et al. Radiosurgery for acoustic neuromas: Results of low-dose treatment. *Neurosurgery*. 2003; 53:282–287. discussion 287–288. [PubMed: 12925242]
30. Vernimmen FJ, Mohamed Z, Slabbert JP, et al. Long-term results of stereotactic proton beam radiotherapy for acoustic neuromas. *Radiother Oncol*. 2009; 90:208–212. [PubMed: 19054586]

Fig. 1. (a) Overall radiologic progression. (b) Progression by baseline volume. (c) Significant radiologic progression by baseline volume. Significant radiologic progression is defined as twice the baseline volume. (FSR = fractionated stereotactic radiotherapy).

Fig. 2.

(a) Tumor in 65-year-old man at time of treatment (approximate baseline volume of 800 mm³). (b) The same tumor after 32 months of follow-up has undergone a 5-fold growth (approximate volume is 4080 mm³). With “freedom from surgical intervention” used as a criterion, this obvious radiologic failure would be considered a success.

Table 1

Demographic and clinical characteristics of patients

Characteristic	All patients (<i>n</i> = 496)	Patients included in volumetric analysis (<i>n</i> = 385)
Age (mean ± SD) (y)	54.0 ± 11.7	54.0 ± 11.5
Male sex [<i>n</i> (%)]	260 (52.4)	202 (52.5)
White race [<i>n</i> (%)]	434 (87.5)	337 (87.5)
Right-sided tumor [<i>n</i> (%)]	270 (54.5)	210 (54.7)
Baseline volume (cm ³)		
Mean ± SD	2.660 ± 4.070	2.647 ± 3.960
Median	0.890	0.930
Interquartile range	0.260–3.420	0.250–3.420
Duration of follow-up (mo)		
Mean ± SD	52.6 ± 25.5	57.5 ± 22.8
Median	52.6	57.4
Interquartile range	32.7–71.5	39.0–73.3
Pretreatment symptoms [<i>n</i> (%)]		
Hearing loss	433 (87.3)	339 (88.0)
Vertigo	83 (16.7)	55 (14.3)
Facial paresthesia	86 (17.3)	74 (19.2)
Facial weakness	12 (2.4)	9 (2.3)
Dysphagia	2 (0.4)	2 (0.5)
Headache	43 (8.7)	31 (8.0)
Nausea	13 (2.6)	12 (3.1)
Otagia	25 (5.0)	17 (4.4)
Ear fullness	85 (17.1)	68 (17.7)
Tinnitus	290 (58.5)	229 (59.5)
Gait imbalance	194 (39.1)	152 (39.5)
Dysgeusia	8 (1.6)	7 (1.8)
Facial twitching	21 (4.2)	13 (3.4)
Diplopia	5 (1.0)	2 (0.5)
Fatigue	3 (0.6)	3 (0.8)
Vomiting	7 (1.4)	7 (1.8)

Table 2

Tumor progression and treatment success and failure for 385 patients with minimum of 18 months of follow-up

Outcome	Baseline volume <1 cm ³	Baseline volume 1 cm ³	Total	% (95% confidence interval)
Therapeutic failure	1	10	11	2.9 (1.4–5.1)
Therapeutic and radiologic success	106	151	258	67.0 (62.1–71.7)
Radiologic progression	56	25	81	21.0 (17.1–25.5)
Significant progression *	33	2	35	9.1 (6.4–12.4)
Total	197	188	385	

* Significant progression defined as twice the baseline volume.

Table 3

Growth in patients with significant radiologic progression

	<i>n</i>	Median volume (range) (mm ³)
Growth ratio *		
2–3	14	82 (30–610)
3–4	7	60 (30–1480)
4–5	5	130 (40–200)
5–10	6	280 (20–1060)
>10	3	100 (60–140)
Total	35	100 (20–1480)

* Growth ratio = Final volume/Pretreatment volume.

Table 4

Significant progression rates by follow-up time

Follow-up time	Significant progression [*] /patients observed during follow-up intervals			Rate of significant progression (95% confidence interval)
	Baseline volume <1 cm ³	Baseline volume 1 cm ³	All patients followed up	
18–36 mo	13/144	1/154	14/298	4.7 (2.6–7.8)
36–18 mo	7/97	1/90	8/187	4.3 (1.9–8.3)
48–60 mo	9/91	0/75	9/166	5.4 (2.5–10.0)
>60 mo	4/142	0/128	4/270	1.5 (0.4–3.7)

^{*} Significant progression defined as twice the baseline volume.

Table 5

Demographic characteristics and pretreatment symptoms for patients by outcome status

	Nonfailures (<i>n</i> = 374)	Failures* (<i>n</i> = 11)	<i>p</i> Value
Age (mean ± SD) (y)	54.3 ± 11.6	51.6 ± 10.2	0.13
Male sex [<i>n</i> (%)]	201 (53.74)	1 (9.09)	0.03
White race [<i>n</i> (%)]	166 (44.9)	11 (100)	0.226
Right-sided tumor [<i>n</i> (%)]	166 (44.39)	8 (72.73)	0.06
Baseline volume (cm ³)			<0.001
Median	0.895	6200	
Interquartile range	0.23–3.310	0.54–14.73	
Duration of follow-up (mo)			<0.001
Median	57.35	23.78 [†]	
Interquartile range	39.0–73.4	22.93–32.11	
Pretreatment symptoms [<i>n</i> (%)]			
Hearing loss	331 (88.5)	8 (72.73)	0.133
Vertigo	54 (14.44)	1 (9.09)	>0.99
Facial paresthesias	69 (18.45)	5 (45.45)	0.041
Facial weakness	9 (2.41)	0 (0)	>0.99
Dysphagia	2 (0.53)	0 (0)	>0.99
Headache	27 (7.22)	4 (36.36)	0.008
Nausea	11 (2.94)	1 (9.09)	0.297
Otalgia	16 (4.28)	1 (9.09)	0.396
Ear fullness	68 (18.18)	0 (0)	0.225
Tinnitus	223 (59.63)	6 (54.55)	0.763
Gait imbalance	145 (38.77)	7 (63.64)	0.121
Dysgeusia	7 (1.87)	0 (0)	>0.99
Facial twitching	12 (3.21)	1 (9.09)	0.318
Diplopia	2 (0.53)	0 (0)	>0.99
Fatigue	3 (0.8)	0 (0)	>0.99
Vomiting	7 (1.87)	0 (0)	>0.99

* Failure defined as salvage surgery (microsurgery).

[†] Time to surgery same as last follow-up for surgically treated patients.