

Tumor pseudoprogression following radiosurgery for vestibular schwannoma

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We sought to characterize vestibular schwannoma (VS) pseudoprogression after radiosurgery to assess its incidence, causative factors, and association with radiation-induced adverse effects. We performed a retrospective study of VS treated with Gamma Knife radiosurgery during 2005–2009. Seventy-five patients had at least 24 months of clinical and radiographic follow-up (median, 29 months) and were included. Tumor response was calculated volumetrically using Gamma plan software on consecutive MRIs. All treatment plans were reviewed for dosimetry characteristics. Forty-nine VS (65%) were stable or regressed after treatment. Seventeen (23%) underwent pseudoprogression, with onset of enlargement at 6 months. Seven (9%) remained larger than initial treatment volume at last follow-up. Nine (12%) had persistent growth. Three patients underwent subsequent microsurgery. One patient required intervention at 3 months for cystic enlargement; otherwise, all patients with progressive enlargement had stable VS until at least 24 months. Twenty-six patients (34.7%) developed nonauditory adverse radiation effects after treatment, including cranial neuropathy, ataxia, and hydrocephalus. There was no statistical association between onset of clinical deterioration and tumor response. Volume changes in the first 24 months after radiosurgery rarely herald treatment failure. Any volume change after 24 months is indicative of treatment failure. Pseudoprogression does not appear to be independently linked to radiation-induced morbidity, and there are no patient-related or radiosurgical parameters that predict tumor response.

Keywords: radiosurgery, tumor response, vestibular schwannoma.

Radiosurgery is a well-established treatment option for selected vestibular schwannomas (VS), with reported tumor control rates of

93%–100%.^{1–9} Although tumor growth with increasing symptoms or neurological deficit may herald treatment failure, the concept of pseudoprogression, or a transient increase in size followed by stability or regression, has been increasingly recognized following radiosurgical treatment of VS and should not be reported as treatment failure. However, although becoming recognized as a true phenomenon, we have a limited understanding about the natural history and predictors of pseudoprogression. In a landmark article in 2006, Pollock described 3 patterns of tumor enlargement after radiosurgery based on linear measurements of VS diameter.¹⁰ In a series of 208 patients, 30 (14%) demonstrated an increase in tumor volume following treatment. Tumor growth was classified as enlargement followed by regression (57%), enlargement without subsequent regression but stable tumor size (29%), and serial growth (14%).

Other case series have also supported the concept of pseudoprogression^{6,11–16} using a variety of methods of tumor measurement, including volumetric analysis.

In the present study, we aim to define the incidence of pseudoprogression following radiosurgery for VS, based on sequential volumetric measurement, and define dosimetric and tumor-related risk factors for pseudoprogression. In addition, we review the current literature on the concept of pseudoprogression in VS to define management recommendations and identify a unified treatment algorithm following stereotactic radiosurgery for VS.

Patients and Methods

We retrospectively reviewed our institutional Gamma Knife treatment database, and a total of 200 patients with VS were treated at the University of Toronto Model 4C Gamma Knife facility (Elekta Instruments, Atlanta, GA) from 2005 through 2009. Of these, 87 patients completed at least 24 months of follow-up. Seven (8%) were excluded for lack of clinical follow-up, and an additional 5 (6%) were excluded from the analysis because of inadequate or incompatible imaging for the volumetric analysis resulting from external MRI

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formats. Approval for this study was granted by the university research ethics board.

All patients were treated with a prescription dose of 12 Gy to the 50% isodose line, and treatments were planned on stereotactic CT and stereotactic contrast-enhanced T1 and T2 MRI sequences using a 1-mm slice thickness.

Subsequent clinical and MRI follow-up visits were scheduled at 3 months, 6 months, 12 months, and then, yearly. For each lesion, the volume was measured at each follow-up MR FIESTA sequence using GammaPlan software. The tumor volume was measured using slice-by-slice manual contouring of coregistered MRIs with a 1-mm slice thickness. A significant change in tumor volume for this study was defined as a 10% change. All volumetric analyses were performed by 2 independent observers, and the mean of the 2 values was used in the analyses. Clinical complications of radiosurgical treatment (cranial neuropathy, ataxia, and hydrocephalus) were documented at each clinic visit.

The clinical data and pretreatment imaging were reviewed for each patient to define pretreatment characteristics to be used for the analysis, including age and tumor morphology (cystic or solid). Tumors were defined as cystic when more than one-third of the tumor mass was hypointense on MRI.

The dosimetric variables studied included Dmax, V100, number of isocenters, maximum dose to brainstem, RTOG conformity index, MDPD (homogeneity index defined as the maximum dose in the treatment volume divided by the prescription dose), gradient index (Paddick¹⁷), and dose rate. All dosimetric values were calculated on the day of treatment and maintained prospectively in a locally developed database.

All statistical analyses were performed using SPSS, version 17 (SPSS Inc., Chicago, IL). A probability of <.05 was defined as statistically significant.

Results

In the 75 patients included in the study, the median age was 58. Three patients in the series had neurofibromatosis type 2, and 9 patients had undergone prior microsurgery. Table 1 shows the patient characteristics. The median tumor volume at treatment was 1.71 cm³ (range, 0.26 cm³–8.19 cm³). Table 2 demonstrates the radiosurgical parameters for the 75 patients. The median follow-up was 29 months (range, 24–60 months). Twenty-six patients (34.7%) developed non-auditory adverse radiation effects following treatment, including trigeminal neuropathy (22%), facial weakness (4%), hydrocephalus (4%), and new ataxia (13%) and 1 patient developed hemifacial spasm.

Tumor Response

Using sequential volumetric measurements, for the purposes of this study, we defined tumor response categories as type 1 (stable), type 2 (tumor regression), type 3

Table 1. Patient characteristics

Variable	Value
Age, years, median (range)	58 (21–84)
VS morphology	Cystic 13 (17.3%) Solid 62 (82.7%)
Sex	Male 31 (41.3%) Female 44 (58.7%)
NF2	3
Prior microsurgery	9
Total follow-up, years, median (range)	29 (24–60)

Table 2. Radiosurgical dosimetry parameters in 75 patients

Variable	Median	Range
Treatment volume (cm ³)	1.71	0.26–8.19
Number of isocenters	11	1–29
Gradient index	2.77	2.4–3.4
Dose rate	2.89	2.54–3.53
V100 (%)	98.3	93.6–99.9
DMax	24	17–34
Conformity index (RTOG)	1.27	1–2.1
MDPD (Homogeneity index)	2	1.43–2.50
Maximum brainstem dose (Gy)	13	2.1–19.7

(initial progression, then stability; pseudoprogression), and type 4 (serial growth). Forty-nine patients (65%) showed tumor stability or regression (types 1 and 2) (Fig. 1). The median volume change in the type 2 group was 53% (range, 10%–88%).

Seventeen patients (23%) had tumor pseudoprogression (type 3). The increase in tumor size occurred at 6 months in all but one patient, who demonstrated enlargement at 12 months. No further enlargement was seen beyond 24 months in any patient in this group. The median change in volume was 23% (range, 10%–81%). Of the 17 patients with pseudoprogression, 7 (41%) tumors remained at the enlarged size at last follow-up, and 10 (59%) had regressed to smaller than the treatment volume at last follow-up (Fig. 2).

Nine patients (12%) had continued tumor enlargement on sequential imaging. The median follow-up in this group was 36 months. The median change in volume in the type 4 response was 67% (range, 10%–507%). Three patients have subsequently undergone microsurgery for symptomatic tumor growth. Only 1 patient demonstrated early significant and symptomatic tumor enlargement, presenting with dramatic enlargement of a cystic VS and undergoing microsurgery at 3 months. The remaining 2 failures requiring microsurgical intervention were declared at 36 and 48 months. Figure 3 shows the overall tumor control in the series. Other than the single early failure with symptomatic cystic enlargement, no patients in this type 4 group demonstrated any tumor enlargement until the 24-month scan.

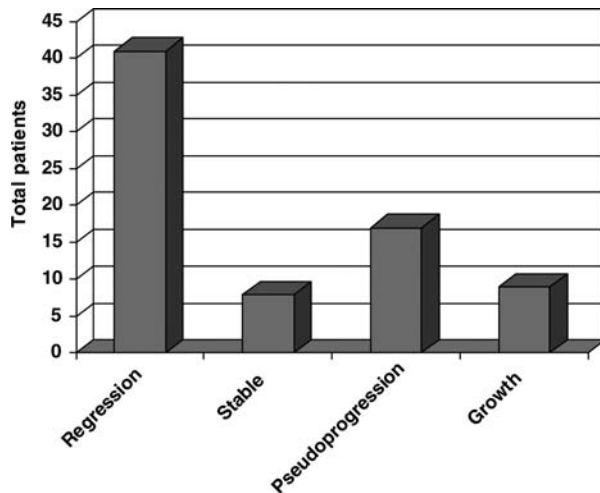


Fig. 1. Bar chart of tumor response in 75 patients.

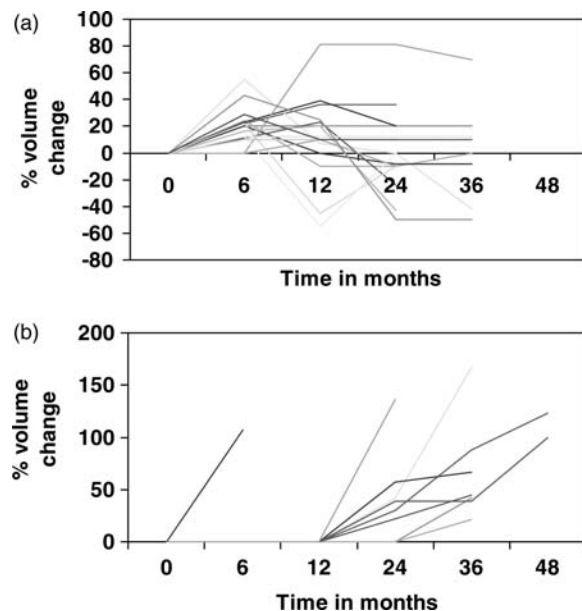


Fig. 2. Line plots of (a) 17 patients with pseudoprogression (type 3), (b) 9 patients with progression (type 4).

There was no association between the category of tumor response and the onset of complications (χ^2 test: $P = .615$).

Predictors of Tumor Response

Tumor response (either stability or growth) was used as the dependent variable for univariate logistic regression analysis, to identify predictors of tumor response. Pretreatment (age and tumor morphology) and dosimetric variables with $P < .10$ in univariate analysis were then included in a multivariate analysis. Although maximum brainstem dose was significant on univariate analysis ($P = .05$), it does not retain significance on multivariate analysis (Table 3). The mean brainstem

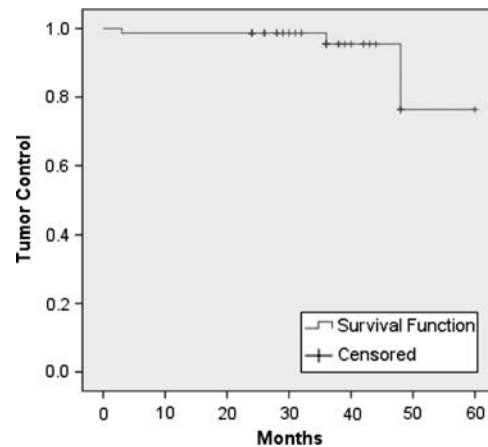


Fig. 3. Kaplan–Meier Curve.

Table 3. Univariate and multivariate analysis for predictors of pseudoprogression

Variable	P-value	
	Univariate	Multivariate
Treatment volume (cm ³)	.24	–
Age at treatment	.39	–
Cystic tumor	.34	–
Gradient index	.88	–
Dose rate	.41	–
MDPD	.63	–
Isocenters	.06	.12
V100	.07	.10
DMax	.94	–
Conformity index	.15	–
Max brainstem dose	.05	.06

dose for those with stable tumors (types 1 and 2) was 12.7 Gy. The mean brainstem dose in those with an increase in tumor volume was 11 Gy. No additional patient or dosimetric variables were predictive of tumor response after radiosurgery.

Discussion

In this series using sequential volumetric assessment, we demonstrate regression of VS following radiosurgery in 55% of tumors. A significant proportion (23%) in this series undergo pseudoprogression, with the onset of enlargement at 6 months. In our series with a median follow-up of 29 months, 9% of tumors remained at a larger size during the period of follow-up available. However, it is important that treatment failure should not be declared because those tumors in this group remain stable beyond 24 months and, moreover, are not associated with a clinical deterioration. Conversely, all those with what we characterize as type 4 tumor response (serial growth), with persistent serial

volume increase, were stable until at least the 24-month scan, except one patient with a cystic VS who had significant symptomatic cystic enlargement at 3 months and underwent microsurgery. We therefore conclude that solid tumors seen to enlarge at 6 months are unlikely to be a treatment failure and that only late enlargement beyond 24 months is indicative of failure.

Considering the number of studies of outcome in radiosurgery for VS, only 8 studies explore the concept of pseudoprogression (Table 4). Of importance, pseudoprogression has been reported in both Gamma Knife- and LINAC-based series, and early radiosurgical series report a 5% rate of transient swelling, or what is now referred to as pseudoprogression.^{1,18} In more recent series, the reported incidence of pseudoprogression following radiosurgery for VS was 17%–74%, using differing methods of measurement.^{6,10,12,14–16,19} The increase in reported rates of pseudoprogression may also reflect a higher awareness of the occurrence of this phenomenon. With use of a multiple linear measurement method to calculate tumor volume, as described by Linskey et al.,²⁰ the reported incidence of tumor enlargement is 14%–54%.^{10,16,21} Van de Langenberg et al. demonstrate that digital segmentation techniques using volumetric software is a more accurate method of assessment of VS growth.²² Nagano et al.¹⁴ reported a 74% rate of tumor expansion following Gamma Knife radiosurgery for VS, with the peak expansion seen at 6.4 months, and 8% of VS remained enlarged up to 5 years following treatment. Most studies, including our series, show that pseudoprogression occurs at 6–9 months following treatment and stabilizes at 2 years.^{10,12–14,21} Therefore, the timing of follow-up imaging is important to differentiate pseudoprogression from treatment failure. Meijer et al.²³ argue that imaging should not be undertaken before 20 months. In our series, those tumors with persistent enlargement did not begin to enlarge until at least 24 months, differentiating them from those with transient swelling as a direct treatment response. This observation would support delaying imaging following

treatment; however, given that in our series and that of Nagano et al.,¹⁴ 9% of VS stabilized at a size greater than the original treatment volume, early imaging is required to differentiate pseudoprogression from true treatment failure. However, we would advocate that, based on our small series and those reported in the literature, no clinical decisions should be made until at least 36 months. Because we have not found clinical symptoms to be associated with tumor response, it would appear to be safe for follow-up imaging to be performed only at 24 months and yearly thereafter.

We defined a 10% threshold change in volume, because previous studies on pseudoprogression have used this criteria.¹⁴ Plotkin et al.²⁴ recommend volumetric measurement of VS for objective response criteria to standardise reporting. They propose a volumetric change of 20% to define clinical response to treatment or progression. In our series, based on a 20% threshold, 17% of tumors showed pseudoprogression, 52% regressed, and 10.6% progressed.

The pathological explanation of pseudoprogression is not precisely known. However, the biological effect of radiosurgery on vestibular schwannoma cells is thought to be a combination of acute inflammation and vascular occlusion.^{25,26} It is therefore not surprising that transient enlargement occurs. Radiation-induced tumor necrosis⁶ and chronic intratumoral hemorrhage²⁷ have been suggested as potential mechanisms, but why this only occurs in a subset of treated VS is unclear. In our series, no clinical or radiosurgical dosimetric parameters were found to be significantly associated with tumor enlargement. Of interest, a lower brainstem dose shows a trend toward subsequent tumor enlargement but does not retain significance in multivariate statistical analysis. Similarly, Nagano et al.¹⁴ showed that a high dose rate was the greatest risk factor for tumor expansion, but this was again not significant in regression analysis. Meijer et al.²³ did not find any patient- or treatment-related factors, such as patient age, tumor volume, or radiation parameters, that could predict tumor progression.

Table 4. VS radiosurgery tumor response literature

Author	Year	Radiation technique	Prescription dose (Gy)	No. patients	Measurement technique	Pseudoprogression %	Max. volume change %	Time to enlargement (months)
Nakamura et al. ¹⁶	2000	GK	13.3	78	Linear volume	42	50	12
Yu et al. ¹²	2000	GK	12	126	Digital volumetric	62	20	6
Okunaga et al. ¹³	2005	LINAC	14	42	Digital volumetric	57	–	4
Hasegawa et al. ¹⁴	2006	GK	13.2	254	Linear volume	10	–	9
Pollock ¹⁰	2006	GK	13.5	30	Linear volume	11	75	9
Meijer et al. ²³	2008	LINAC	12.5	45	Digital volumetric	31	25	–
Delsanti et al. ²¹	2008	GK	12	332	Linear volume	54	–	6
Nagano et al. ¹⁴	2008	GK	12	100	Digital volumetric	74	50	6.4

In our series, there was no significant association between postradiosurgical clinical deterioration (cranial neuropathy, ataxia, and hydrocephalus) and tumor response. There was an overall rate of adverse effects of 34.7% among patients. Pollock reports that 20% of patients had symptoms noted at the time of tumor enlargement, but the number of adverse effects seen in those without tumor enlargement is not reported in this series.¹⁰ Nagano et al.¹⁴ found that there was a significant difference in the rate of facial dysesthesia, facial weakness, and hemifacial spasm when comparing patients with a >30% transient increase in tumor volume with those with a <30% transient increase in volume.

Conclusion

Tumor pseudoprogression should be anticipated and not considered to be treatment failure. In our series, 23% of VS treated with radiosurgery underwent

pseudoprogression, with onset at 6 months and, most commonly, regression by 24 months. VS that begin to enlarge only after 24 months are likely to be treatment failure, and a second intervention should be considered only at this stage.

In our series, there was no association between transient tumor enlargement and clinical deterioration. Therefore, we would advocate baseline imaging only to document the maximum stable size of VS after radiosurgery, and no salvage therapy should be instituted before 36 months, unless there is clinical need to intervene.

We did not identify any clinical or dosimetric parameters that could predict tumor pseudoprogression in our series. Further studies are required to understand the biological mechanisms of tumor pseudoprogression and to identify clinical predictors of this phenomenon.

Conflict of interest statement. None declared.

References

- Noren G, Greitz D, Hirsch A, Lax I. Gamma knife surgery in acoustic tumours. *Acta Neurochir Suppl (Wien)*. 1993;58:104–107.
- Kobayashi T, Tanaka T, Kida Y. The early effects of gamma knife on 40 cases of acoustic neurinoma. *Acta Neurochir Suppl*. 1994;62:93–97.
- Valentino V, Raimondi AJ. Tumour response and morphological changes of acoustic neurinomas after radiosurgery. *Acta Neurochir (Wien)*. 1995;133(3–4):157–163.
- Lunsford LD, Niranjan A, Flickinger JC, Maitz A, Kondziolka D. Radiosurgery of vestibular schwannomas: summary of experience in 829 cases. *J Neurosurg*. 2005;102(Suppl):195–199.
- Miller RC, Foote RL, Coffey RJ, et al. Decrease in cranial nerve complications after radiosurgery for acoustic neuromas: a prospective study of dose and volume. *Int J Radiat Oncol Biol Phys*. 1999;43(2):305–311.
- Prasad D, Steiner M, Steiner L. Gamma surgery for vestibular schwannoma. *J Neurosurg*. 2000;92(5):745–759.
- Flickinger JC, Kondziolka D, Niranjan A, Lunsford LD. Results of acoustic neuroma radiosurgery: an analysis of 5 years' experience using current methods. *J Neurosurg*. 2001;94(1):1–6.
- Spiegelmann R, Lidar Z, Gofman J, Alezra D, Hadani M, Pfeffer R. Linear accelerator radiosurgery for vestibular schwannoma. *J Neurosurg*. 2001;94(1):7–13.
- Foote KD, Friedman WA, Buatti JM, Meeks SL, Bova FJ, Kubilis PS. Analysis of risk factors associated with radiosurgery for vestibular schwannoma. *J Neurosurg*. 2001;95(3):440–449.
- Pollock BE. Management of vestibular schwannomas that enlarge after stereotactic radiosurgery: treatment recommendations based on a 15 year experience. *Neurosurgery*. 2006;58(2):241–248; discussion 241–248.
- Noren G. The Gamma Knife and acoustic tumors. *Med Health R I*. 1996;79(6):232–235.
- Yu CP, Cheung JY, Leung S, Ho R. Sequential volume mapping for confirmation of negative growth in vestibular schwannomas treated by gamma knife radiosurgery. *J Neurosurg*. 2000;93(Suppl 3):82–89.
- Okunaga T, Matsuo T, Hayashi N, et al. Linear accelerator radiosurgery for vestibular schwannoma: measuring tumor volume changes on serial three-dimensional spoiled gradient-echo magnetic resonance images. *J Neurosurg*. 2005;103(1):53–58.
- Nagano O, Higuchi Y, Serizawa T, et al. Transient expansion of vestibular schwannoma following stereotactic radiosurgery. *J Neurosurg*. 2008;109(5):811–816.
- Hasegawa T, Kida Y, Yoshimoto M, Koike J, Goto K. Evaluation of tumor expansion after stereotactic radiosurgery in patients harboring vestibular schwannomas. *Neurosurgery*. 2006;58(6):1119–1128; discussion 1119–1128.
- Nakamura H, Jokura H, Takahashi K, Boku N, Akabane A, Yoshimoto T. Serial follow-up MR imaging after gamma knife radiosurgery for vestibular schwannoma. *AJNR Am J Neuroradiol*. 2000;21(8):1540–1546.
- Paddick I, Lippitz B. A simple dose gradient measurement tool to complement the conformity index. *J Neurosurg*. 2006;105(Suppl):194–201.
- Pollock BE, Lunsford LD, Noren G. Vestibular schwannoma management in the next century: a radiosurgical perspective. *Neurosurgery*. 1998;43(3):475–481; discussion 481–473.
- Wowra B, Muacevic A, Jess-Hempfen A, Hempel JM, Muller-Schunk S, Tonn JC. Outpatient gamma knife surgery for vestibular schwannoma: definition of the therapeutic profile based on a 10-year experience. *J Neurosurg*. 2005;102(Suppl):114–118.
- Linskey ME, Lunsford LD, Flickinger JC. Neuroimaging of acoustic nerve sheath tumors after stereotactic radiosurgery. *AJNR Am J Neuroradiol*. 1991;12(6):1165–1175.

21. Delsanti C, Roche PH, Thomassin JM, Regis J. Morphological changes of vestibular schwannomas after radiosurgical treatment: pitfalls and diagnosis of failure. *Prog Neurol Surg.* 2008;21: 93–97.
22. van de Langenberg R, de Bondt BJ, Nelemans PJ, Baumert BG, Stokroos RJ. Follow-up assessment of vestibular schwannomas: volume quantification versus two-dimensional measurements. *Neuroradiology.* 2009;51(8):517–524.
23. Meijer OW, Weijmans EJ, Knol DL, et al. Tumor-volume changes after radiosurgery for vestibular schwannoma: implications for follow-up MR imaging protocol. *AJNR Am J Neuroradiol.* 2008;29(5): 906–910.
24. Plotkin SR, Halpin C, Blakeley JO, et al. Suggested response criteria for phase II antitumor drug studies for neurofibromatosis type 2 related vestibular schwannoma. *J Neurooncol.* 2009;93(1):61–77.
25. Linskey ME, Lunsford LD, Flickinger JC. Radiosurgery for acoustic neurinomas: early experience. *Neurosurgery.* 1990;26(5):736–744; discussion 744–735.
26. Witham TF, Okada H, Fellows W, et al. The characterization of tumor apoptosis after experimental radiosurgery. *Stereotact Funct Neurosurg.* 2005;83(1):17–24.
27. Iwai Y, Yamanaka K, Yamagata K, Yasui T. Surgery after radiosurgery for acoustic neuromas: surgical strategy and histological findings. *Neurosurgery.* 2007;60(2 Suppl 1):ONS75–82; discussion ONS82.