Stereotactic Radiosurgery versus Natural History in Patients with Growing Vestibular Schwannomas

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J Neurol Surg B 2015;76:286–290.

Abstract

Objective To describe our experience with stereotactic radiosurgery and its efficacy on growing tumors, and then to compare this result with the natural history of a similar cohort of non-radiation-treated lesions.

Study Design A retrospective chart review and cohort comparison.

Methods The long-term control rates of patients having undergone radiosurgery were collected and calculated, and this population was then compared with a group of untreated patients from the same period of time with growing lesions.

Results A total of 61 patients with growing vestibular schwannomas treated with radiosurgery were included. After a mean of 160 months, we observed a control rate of 85.2%. When compared with a group of 36 patients with growing tumors who were yet to receive treatment (previously published), we found a corrected control rate or relative risk reduction of only 76.8%.

Conclusion Radiosurgery for growing vestibular schwannomas is less effective than previously reported in unselected series. Although radiosurgery still has a role in managing this disease, consideration should be given to the actual efficacy that may be calculated when the natural history is known. We hope other centers will similarly report their experience on this cohort of patients.

Keywords

- radiosurgery
- natural history
- vestibular schwannomas
- control rates
- growing tumors

Introduction

Vestibular schwannomas are relatively uncommon histologically benign intracranial tumors. Management of these lesions is multidisciplinary and may include observation, microsurgical resection, radiosurgery, or a combination of modalities. The most appropriate treatment is determined by patient and lesion characteristics. In general, larger lesions are more likely to undergo microsurgical resection, whereas smaller lesions may be managed with observation or radiosurgery.

Reported lesion control rates with radiosurgery range from 85% to 100%.^{1–4} These series, however, contain several limitations including a short follow-up and inclusion of unselected patients having tumors without demonstrated growth. Additionally, control rates in general have previously been determined from case series with no attempt to find a reasonable comparison group, assuming all untreated tumors were going to grow. Recent natural history studies have revealed that following diagnosis, up to 60% of lesions remain quiescent and nearly 20% shrink in size.^{5–9} Even in tumors

received

July 1, 2014

accepted

November 28, 2014

published online

March 2, 2015

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Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0034-1544117>.
ISSN 2193-6331.

with demonstrated growth, only 47 to 64% continue to enlarge with continued conservative management.¹⁰

In patients with isolated hearing loss in the absence of any other neurologic deficit, observation may be a reasonable strategy with intervention offered only for patients with tumors that are shown to grow or cause neurologic sequelae. In practice, however, no consistent indices are available to predict reliably which lesions will progress. By failing to account for lesions with a quiescent natural history, the efficacy of radiosurgery for growing tumors may be less than currently perceived.

We reviewed a single-institution experience with vestibular schwannomas that had been selected for treatment due to documented growth. Long-term results after radiosurgery for these lesions is compared with our previously reported experience with the natural history of growing tumors determined from patients waiting for surgery.¹⁰

Materials and Methods

Approval of the study protocol was obtained from the institutional clinical research ethics review board before initiation of the study. The three senior authors (B.D.W., R.A., and B.T.) represent the neuro-otology, neurosurgery, and radiosurgery team at a quaternary referral center for patients with vestibular schwannomas.

A retrospective review was performed of all patients who underwent radiosurgery for growing vestibular schwannomas at our institution (The British Columbia Cancer Agency). A list of all patients with the diagnosis of vestibular schwannoma treated with linear accelerator (LINAC) radiosurgery at the British Columbia Cancer Agency between July 1994 and January 2004 was obtained from medical records based on *International Classification of Diseases*, 9th edition (ICD-9) codes. Radiosurgery was administered using a LINAC platform. All patients received a prescription of a single fraction of 12 Gy at the 80% isodose line.

Patients who underwent fractionated radiotherapy in an effort to preserve their hearing were excluded from this analysis, as were those with a neurocutaneous disorder (i.e., neurofibromatosis) or previous radiosurgery.

Two authors (P.G. and A.T.) reviewed the patient imaging. Radiologic assessment of tumor size and growth rate was primarily undertaken with high-resolution magnetic resonance imaging (MRI) (gadolinium-enhanced and fast imaging employing steady-state acquisition sequence images). Contrast-enhanced computed tomography (CT) was performed in some patients early in the series. At our center, patients received clinical and radiographic follow-up every 6 to 12 months after treatment. Tumor size was measured as the greatest extracanalicular dimensions on anterior-posterior, sagittal, and coronal dimensions. Intracanalicular tumors were measured by the greatest intracanalicular anterior-posterior, sagittal, and coronal dimensions. If imaging was unavailable, a documented interval change in size as reported by a neuroradiologist was also accepted for inclusion. Positive growth was defined as > 1 mm in any dimension, and negative growth was defined as a decrease > 1 mm. This definition of radiographic change was

based on a previous study at our institution assessing the interobserver and intraobserver reliability of MRI scan measurements (Ngo et al, unpublished data). A minimum of 18 months posttreatment follow-up was necessary to avoid mistaking transient postradiosurgery expansion growth. Additionally, a stringent definition of treatment failure was used such that tumor growth following radiosurgery was deemed significant if it resulted in a rereferral of the patient for consideration of salvage surgery.

Patients with radiosurgery-treated tumors were compared with patients on our surgical waiting list who had yet to undergo any treatment. These individuals were described in detail previously.¹⁰ This group was identified by reviewing billing records (ICD-9 codes) of the primary author from 1994 to 2007. Inclusion criteria similarly comprised the presence of a unilateral vestibular schwannoma with radiographically documented growth > 1 mm on two consecutive MRI or CT studies. Patients with previous surgery/radiosurgery, recurrent tumors, or neurocutaneous disorders (i.e., neurofibromatosis 1 or 2) were likewise excluded. A Student *t* test was used to compare characteristics of the radiosurgery- and nonradiosurgery-treated groups.

Results

A total of 96 patients were treated with single-fraction radiosurgery for a vestibular schwannoma during the period of interest. Thirty patients were excluded for incomplete records (i.e., no verification of lesion size, no confirmation of lesion growth). Five patients were excluded for the presence of bilateral tumors. All patients had > 36 months of follow-up. In total, 61 fit inclusion criteria (► **Fig. 1**). In comparison, 487 patients were identified from our surgical consultation database over the same period of interest. Overall, 36 of these patients were found to have a radiologically confirmed growing tumor in the absence of prior treatment or neurocutaneous disorder.¹⁰

Radiosurgery patients ranged in age from 24 to 80 years with a mean of 65 years; 53% were female. Overall follow-up duration was 108 to 216 months with a mean of 160 months. The average period over which lesion growth was detected was 25.7 months after radiation. Three patients had previous microsurgical resection before radiosurgery. The average pretreatment maximal diameter

Fig. 1 Flow diagram depicting the screening criteria for radiosurgery patient entry and exclusion from study.

was 19.1 mm, and posttreatment was 15.6 mm (►Table 1). In comparison, natural history patients ranged from 30 to 85 years of age with a mean of 60.1 years; 47% were female. Mean follow-up in this group was only 25 months (as all subsequently had surgery). None underwent prior surgery or radiosurgery. The mean initial tumor diameter was 14.1 mm. With the exception of the follow-up duration, the differences between radiosurgery and natural history groups were nonsignificant.

A total of 65.6% of the tumors (40) decreased in size after radiosurgery; 19.7% of the tumors (12) remained stable. Overall, 14.8% of the tumors (9) grew and were subsequently rereferred for surgery (rereferral for surgery was defined as treatment failure). Although growth was demonstrated an average of 25.7 months after radiosurgery as mentioned previously, rereferral for surgical salvage was seen after a mean of 48.7 months, demonstrating our stringent definition of treatment failure. Overall treatment success defined as reduction or stabilization in tumor size was 85.2%. In contrast, 5.6% of tumors (2) in the natural history group shrank in size, 30.6% (11) remained stable, and 63.9% (23) continued to grow. All of these patients in the natural history group eventually underwent surgical resection (because these patients were compiled from a surgical waiting list). There were no significant differences in pretreatment size between radiosurgery and natural history tumors (►Table 2).

A total of 23% of patients (14) experienced one or more adverse events after radiosurgery (►Table 3), although most were mild and transient. Overall, 19.6% of patients (12) had temporary facial paresthesias or balance changes. Two patients (3.3%) developed hydrocephalus, however, and required cerebrospinal fluid diversion. One patient (1.2%) had a concurrent lesion (i.e., meningioma) that became symptomatic during follow-up and required a craniotomy for its removal. One patient (1.2%) developed dementia and withdrew from further assessment 60 months after treatment. Another patient died from unrelated causes after 23 months.

Discussion

Since inception, our group's modus operandi has been only to treat lesions shown to be growing. Although radiosurgery is established in the management of multiple pathologies and offers advantages in patients for whom lesion stabilization is satisfactory, it is not entirely without risk.^{1,11-14} Significant complications such as malignant degeneration, secondary neoplasms, and radionecrosis have been reported.¹⁵⁻²⁰ Hussein et al further observed that previous treatment with radiosurgery compounds the difficulty associated with salvage resection of these lesions.²¹ Furthermore, our own observation of patients with stable lesions has led us to question whether the efficacy of many interventions, including radiosurgery, has been overstated.

Published series of patients undergoing radiosurgery for vestibular schwannomas have reported control rates of 79 to 96.4% with most groups describing > 90% control at 5 years.^{1-3,15} These studies are unselected, however, and likely included tumors with a favorable natural history, thereby overestimating the actual efficacy of radiosurgery. From our results, we appreciate a lower than expected control rate when nonprogressing lesions are excluded. While reviewing the literature, we have been unable to find any studies that contain a control or natural history group to compare the true effectiveness of radiation treatments.

Previous natural history series and our own published work have suggested that the strongest predictor for ongoing growth is initial growth on interval imaging.^{5,9,10,22} Of patients with growing lesions, 47.5 to 64% have been reported to continue to grow during follow-up.^{5,9,10,22} Stangerup et al further found that lesions growing in the first year demonstrated a more rapid growth rate than those observed to grow on a delayed basis.⁵ Although a few studies of growing vestibular schwannomas exist, these lesions appear to demonstrate a more aggressive progression. Varughese et al reported that radiosurgery slowed the growth rate on all treated tumors despite some continuing to progress; this finding was not investigated further in this study.²³

Table 1 Patient and tumor demographics

	<i>n</i>	<i>n</i>	<i>p</i> value
	Radiation treated	Natural history ⁸	
No. patients	61	36	NA
Male/Female	29/32	19/17	0.41
Age range, y	24–80	30–85	NA
Mean age, y	65	60.2	0.50
Mean follow-up duration, total, mo	160	25	< 0.01
Mean follow-up duration, pretreatment, mo	29	25	0.59
No. of patients with prior resection	3	0	NA
No. of patients without prior treatment	58	36	NA
Maximal mean pretreatment diameter, mm	19.1	14.3	0.71
Maximal mean posttreatment diameter, mm	15.6	NA	NA

Abbreviation: NA = not applicable.

Table 2 Comparison of radiation-treated and natural history population of tumors

	Radiation treated	Natural history ⁸	p value
No. shrink, % (n)	65.6 (40)	5.6 (2)	< 0.0001
No. stable, % (n)	19.7 (12)	30.6 (11)	0.11
No. grow, % (n)	14.7 (9)	63.9 (23)	< 0.001
Mean time to progression after radiosurgery, mo	48.7	NA	NA
No. referred for further intervention, that is, surgery, % (n)	14.7 (9)	100 (31)	
Mean treatment size of lesions that shrank, mm	18.2	17.4	0.76
Mean treatment size of lesions that remained stable, mm	18.5	11.5	0.75
Mean treatment size of lesions that grew, mm	15.4	12.1	0.14

Abbreviation: NA = not applicable.

Table 3 Adverse events in radiosurgery-treated patients

Adverse event	n
Headache	3
Balance changes	6
Hydrocephalus	2
Trigeminal nerve dysfunction	7
Facial nerve dysfunction	0
Tinnitus	1

In general, when a control rate is reported, it is interpreted as an absolute risk reduction (ARR) with the assumption that all untreated tumors are going to grow (i.e., 100% of tumors minus 14.8% progressing tumors equals 85.2% control rate, or ARR). We know that even in the case of growing vestibular schwannomas, not all will continue to progress. From our natural history population, we can calculate a corrected absolute risk reduction rate (cARR) by taking the difference between natural history progression rate and radiosurgery-treated progression rate (i.e., 63.9% [from our natural history group] minus 14.8% [from our radiosurgery-treated group]) that gives a cARR of 49.1%. We can also determine a relative risk reduction (RRR) by comparing the same results. Relative risk is determined by comparing the cARR (i.e., 49.1%) to the natural history progression rate (i.e., 63.9%), which from our observations is actually only 76.8% (i.e., cARR/[natural history progression rate] = [49.1%/63.9%] = 76.8%) (►Table 4).

We can further perform similar calculations using numbers obtained from the literature regarding control rates in unselected series. The natural history growth rates in the literature can be used as a control for reported radiosurgery series to calculate a RRR. For example, if we assume the control rate with radiosurgery in unselected series is ~ 95% (a commonly reported control rate) and the natural history of unselected series is for only ~ 30% to grow (commonly reported natural history growth rate), then using the previously described approach we find an ARR of 25% (i.e., 30% minus [1 minus 95%]) and a RRR (i.e., 25%/30%) of only 83%. By reporting a RRR (i.e., 83%), we believe that this information more accurately reflects the efficacy of radiosurgery in the context of a group of tumors whose natural history includes nonprogression.

We recognize that this study includes only a limited number of patients from a single institution. Furthermore, we acknowledge that our cohorts are not directly comparable. From a practical standpoint, our natural history cohort represented a

Table 4 Calculated control rates and risk reduction in radiation-treated and natural history groups

	Radiation treated, %	Natural history, % ¹⁰	p value
Observed control rate	85.20	36.12	< 0.001
Observed progression rate	14.80	63.90	< 0.001
Expected progression rate (from Mick et al ¹⁰)	63.90	NA	NA
Absolute risk reduction	49.10	NA	NA
Relative risk reduction/Corrected control rate	76.80	NA	NA

Abbreviation: NA = not applicable.

group of patients awaiting surgical intervention, and further natural history follow-up would have not been feasible. Given the much shorter follow-up of the natural history group, we believe with further follow-up that more of the stable tumors would have grown. This would have given us an actual control rate between 76.8% and 85.2%, which would still be much lower than the commonly quoted control rates from unselected series of tumors. We are, however, attempting to create a reasonable best comparison that has been, to our knowledge, lacking in previous reports. Our natural history group was triaged and treated during the same period in the same institution, and we believe it offers a reasonable standard to which we may juxtapose our radiosurgery outcomes. Furthermore, when we compare only the pretreatment time interval for the radiosurgery-treated group, we find the follow-up periods are actually very similar. The control rate reported here is comparable with those reported after radiosurgery in patients with neurofibromatosis type 2 who are known to have more clinically aggressive lesions.⁴

Conclusion

Radiosurgery appears to be less effective in patients with documented growing vestibular schwannomas than what was previously described in unselected series. At our institution, we believe actual control rates are between 76.8% and 85.2%. This is also supported by simple mathematical correction that can be made using control rates and natural history rates for unselected series from the literature (83%; see Discussion). Although still beneficial, the role for radiation should be balanced against the potential complications and difficulties encountered as well as with natural history. In attempting to critically evaluate the effect of radiosurgery we sought to have a comparison group and believe that actual control rates are lower than what is currently reported. These results will need to be confirmed by other experienced institutions. When deciding on a course of best treatment, a clinician should review the outcomes of different treatments from their own institution because local experience may vary significantly.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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