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What is This?
Three-Dimensional Segmented Volumetric Analysis of Sporadic Vestibular Schwannomas: Comparison of Segmented and Linear Measurements

Patrick C. Walz, MD1, Matthew L. Bush, MD1,2, Zachary Robinett3, Claudia F. E. Kirsch, MD4, and D. Bradley Welling, MD, PhD1

Abstract

Objective. To compare 3-D segmented volumetric analysis of vestibular schwannomas (VS) with traditional linear tumor measurement on serial magnetic resonance imaging (MRI) studies to assess volume and growth rates.

Study Design. Case series with retrospective chart review.

Setting. Tertiary care medical center.

Methods. This analysis identified 24 VS patients clinically followed with serial gadolinium enhanced images. Maximum linear dimensions (MLD) were obtained from gadolinium-contrasted T1 sequences from 3 serial MRI scans per RECIST guidelines. MLD was cubed (MLD3) and orthogonal analysis (OA) was carried out to provide volumetric estimates for comparison with segmented data. Segmented volumetric analysis (SVA) was performed with semi-automated 3-D conformal procedure. Tumor volume, percentage change in volume, and interval percentage change were compared using paired 2-tailed t tests.

Results. The average interval between MRIs was 2.6 years. Volume estimates differed significantly between SVA and OA and MLD3 at all intervals. Linear growth measurements averaged 0.5 mm/y (5.4%). Volumetric growth was 50 mm3/y (22.8%) with SVA, 110 mm3/y (19.6%) with OA, and 210 mm3/y (14.4%) with MLD3 estimates. Differences between MLD and both MLD3 and SVA were significant, but significance between MLD3 and SVA was only identified in interval analysis. Progression was identified in 75% more patients with SVA than OA, MLD3, or MLD.

Conclusions. VS assume complex configurations. Linear measurements inaccurately estimate tumor volume and growth compared with segmented analysis. SVA is a useful clinical tool that accurately assesses tumor volume. Use of outcomes such as tumor volume and percentage of volume change may be more sensitive in assessing tumor progression compared with linear measurements.

Keywords

vestibular schwannoma, volumetric analysis, acoustic neuroma, growth assessment, magnetic resonance imaging

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Conservative management of select vestibular schwannoma (VS) with the “wait and scan” method is a commonly used strategy in the neurotologic and neurosurgical fields. Followed with serial magnetic resonance imaging (MRI), tumor growth is estimated and symptomatic change is assessed to determine the appropriateness of continued conservative management versus surgical or radiotherapeutic intervention. The current standard of care in assessment of VS is assessment of maximum linear dimensions,1 as this method is quick and simple, allowing rapid application in the clinical setting. Previous efforts have estimated sporadic VS growth characteristics using this method and attempted to correlate growth with clinical outcomes.2,3 Unfortunately, this method of measurement is known to be limited due to poor correlation with actual tumor volume, high intraobserver variability, and systematic underestimation of small tumor volume in conjunction with overestimation of large tumor volume.4 With these drawbacks, it is necessary to...
adopt a more accurate method of assessment of tumor burden and change over time in order to appreciate VS behavior and appropriately counsel patients.

Segmented volumetric analysis is an established method of assessing VS tumor burden and tumor growth. Much investigation has evaluated the role of volumetric analysis in the management of neurofibromatosis type II (NF-2) and in follow-up after stereotactic radiotherapy, while few efforts have focused on sporadic schwannomas. In 1999, Niemczyk and colleagues established the accuracy of semiautomated computerized segmented volumetric analysis, using wax phantoms to determine the accuracy of volumetric analysis to within 10% of actual tumor volume. Previous authors have used segmented volumetric assessments to evaluate groups of tumors that include both sporadic and NF-2, but specific differences in tumor growth rate have been noted when comparing vestibular schwannomas in the setting of NF-2 and sporadic VS. Prior segmented volumetric assessments focused on sporadic VS have evaluated hearing outcomes related to VS volume and prediction of growth, but there have been few direct comparisons of linear estimates of volume and segmented volumetric calculations in the sporadic VS population.

We hypothesized that segmented volumetric analysis would more accurately identify both tumor volume and VS progression in sporadic VS and tested this hypothesis by retrospectively collecting a sample of MRIs from wait and scan patients.

**Patients and Methods**

**Patient selection.** Prior to proceeding, institutional review board approval for the project was obtained for the protocol titled “Comparison of Three Dimensional versus Linear Surveillance Imaging Techniques for Serial Observation of Vestibular Schwannomas,” protocol number 2008H0263 from the Biomedical Sciences Institutional Review Board. An ICD-9 code search of patients who presented to our tertiary care medical center for evaluation of a vestibular schwannoma (225.1) and selected the wait and scan management strategy between 1990 and 2010 was performed, and these patients were included. Patients with fewer than 3 consecutive MRIs were excluded. A total of 586 VS patients were evaluated, 134 of whom initially elected the wait and scan management strategy, 6 had cerebellopontine angle tumors inconsistent with VS, and 1 was unable to undergo MRI secondary to prosthetic incompatibility. Analysis was performed on 72 MRI scans for the remaining 24 patients, with an average time span between serial MRI scans of 1.31 years. The wait and scan method was decided on because of advanced patient age (9), minimal symptoms (7), significant medical comorbidities (3), or patient preference (5).

**Imaging.** Gadolinium-contrast T1 sequences, 0.7 (n = 4) and 1.5 (n = 68) Tesla in strength, were utilized for comparison and measurements. Spoiled gradient recall (SPGR) sequences were used when available (n = 60). In instances of outside imaging where SPGR sequences were not obtained, contrast enhanced T1 images with fine cuts through the internal auditory canal were utilized (n = 12). When patients obtained outside imaging, these institutions were contacted and digital copies were obtained when possible and loaded into the local picture archiving and communication system (PACS). Slice thickness ranged from 0.8 to 3.0 mm.

**Maximum linear diameter (MLD) measurements (Figure 1).** Greatest linear measurement in the anteroposterior, transverse, and craniocaudal planes for each lesion at 3 time points was collected using AquariusNet viewer (Foster City, California) according to RECIST guidelines. Measurements were completed in triplicate and average values were utilized for comparison and analysis. The maximum linear dimension for each scan was used for the remainder of analysis. MLD corresponded to the transverse dimension in 65 scans, anteroposterior dimension in 2 scans, and craniocaudal dimension in 5 scans.

**Cubed maximum linear diameter (MLD³) measurements.** In order to compare volumetric data head to head, MLD was cubed to provide a volumetric estimate for analysis, per Harris et al.

**Orthogonal analysis (OA).** The maximum linear measurements in the anteroposterior, crano-caudal, and transverse planes were multiplied to give a second volumetric estimate using linear measurements. Extension into the internal auditory canal was included in measurements when this occurred.

**Segmented volumetric analysis (Figure 2).** Segmented volumetric analysis (SVA) was performed with semiautomated

**Figure 1.** Linear measurements. Maximum linear diameter (transverse line) was measured in the axial and coronal planes on T1, gadolinium enhanced SPGR MRI sequences.
3-D conformal volumetric analysis using the Terarecon Aquarius workstation (Foster City, California). For each patient, the tumor was manually outlined in the axial plane in all sections for each study and a segmented volumetric model was created with computerized compilation of each slice’s volume and assessment of total tumor volume. Segmented volumetric models were re-reviewed after analysis to ensure accuracy.

**Statistical analysis.** All data were collected in an electronic spreadsheet (Microsoft, Redmond, Washington). Volumes calculated by MLD³, OA, and SVA were compared at each time point via paired 2-tailed t tests. Gross, percentage, and annual change in tumor volume by SVA, OA, and MLD³ were calculated and compared using paired 2-tailed t tests. Annual and percentage change were calculated for linear measurements and volumetric data and compared using paired 2-tailed t tests. Significance was set at \( P < .05 \). Progression was defined as \( > 73\% \) change in volume or \( > 20\% \) change in linear dimension, as identified by Prasad et al¹³ and applied to VS by Harris et al.⁶

**Results**

**Patient characteristics.** Average age at presentation was 61.9 years (range, 18-81 years). Presenting symptoms are reviewed in **Table 1**. Of the serially observed patients, 1 (4.2%) required subsequent surgical resection due to continued growth of the vestibular schwannomas while 2 (8.4%) elected to proceed undergo stereotactic radiotherapy. Additional demographic details are described in **Table 1**.

**Vestibular schwannoma volume.** Average volumes at each time point for SVA, OA, and MLD³ are displayed in **Figure 3**. Average volume for SVA was \( 0.26 \pm 0.21 \text{ cm}^3 \), \( 0.31 \pm 0.24 \text{ cm}^3 \), and \( 0.36 \pm 0.25 \text{ cm}^3 \) at each respective time point versus \( 1.76 \pm 2.15 \text{ cm}^3 \), \( 1.89 \pm 2.06 \text{ cm}^3 \), and \( 2.14 \pm 2.28 \text{ cm}^3 \) with MLD³ and \( 0.57 \pm 0.6 \text{ cm}^3 \), 0.70 ± 0.75 cm³, and 0.80 ± 0.83 cm³ with OA. Differences at each time point were significant when comparing SVA to MLD³ \( (P = .001, .0003, \text{ and } .0003, \text{ respectively} \) and OA \( (P < .002 \text{ at each time point} \).

**Vestibular schwannoma growth.** VS growth estimated by MLD measurements averaged \( 0.5 \pm 0.7 \text{ mm/y} \) (range, 0-2.4 mm/y), corresponding to a 5% average change per year. MLD³ assessment estimated tumor volume increase at a rate of \( 210 \text{ mm}^3/y \) (14.4%) with OA estimating tumor volume increase at \( 110 \text{ mm}^3/y \) (19.6%) while SVA estimated average tumor growth rate was \( 50 \text{ mm}^3/y \) (22.8%).

**Gross change in vestibular schwannoma.** MLD measurements revealed a 9.4% ± 22.3% change in size from initial to final scan compared to 57.2% ± 92% for SVA measurements, 51.9% ± 89.7% for OA, and 49.3% ± 119.5% for MLD³. The differences between MLD and MLD³, MLD³ and SVA, SVA and OA, and MLD³ and OA were not significant \( (P = .058, .73, .72, \text{ and } .84, \text{ respectively} \) while the differences between MLD and SVA and MLD and OA did reach significance \( (P = .01 \text{ and } .01, \text{ respectively} \). When calculating these measures for discrete intervals from MRI to MRI, OA, MLD³, and SVA methods differed significantly from MLD in the first interval \( (P = .024, .047, \text{ and } .029, \text{ respectively} \) while SVA measures differed significantly from both MLD and MLD³ in the second interval \( (P = .017 \text{ and } .01, \text{ respectively} \) (**Figure 4**). OA measures differed significantly from MLD and MLD³ in the second interval as well \( (P = .02 \text{ and } .006, \text{ respectively} \), but did not differ significantly from SVA \( (P = .5) \).
Table 1. Demographic Data for Study Population

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<td>—</td>
<td>4.2</td>
</tr>
<tr>
<td>Pressure</td>
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</tr>
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</table>

Abbreviation: SRT, stereotactic radiotherapy.

![Figure 3](image_url)

**Figure 3.** Volume measurements with segmented volumetric analysis (SVA), orthogonal analysis (OA), and cubed maximum linear dimension (MLD). *Denotes statistically significant difference from OA and † denotes significant difference from SVA (P < .001 for all values).

**Annual percentage change in vestibular schwannoma.** Adjusting for duration between MRIs demonstrated significant differences between MLD and MLD* (P = .041) over the duration of the study, with no other changes in significance (Figure 4).

**Vestibular schwannoma progression.** Using Harris et al.’s criteria,6 7 VS were found to progress over the study period using SVA measurements while OA, MLD, and MLD* only identified 4 progressing tumors (Figure 5).

**Discussion**

In the clinical setting, discussions of therapeutic options between physician and patient rely heavily on prognostic indicators that can be gleaned from careful analysis of available data. In selecting candidates for the wait and scan policy and continuing this management strategy, an accurate assessment of true tumor volume and change over time is imperative to appropriately counsel patients regarding expected outcomes. Many previous authors have sought to identify specific VS growth patterns,1 imaging characteristics,3,10 and clinical indicators10,11 to identify tumors that are not likely to progress over time and have identified increased size, presence of tinnitus,3 hypodensities within the tumor,10 age, sex, and several other factors as potential predictors of growth. Recent systematic review and meta-analysis of the available literature, however, has revealed no reliable predictors of VS growth.14 Massick et al noted that tumor growth corresponded to progression of hearing deterioration regardless of size of VS at presentation,11 while more recent work by Van de Langenberg et al has noted that volumetric changes in VS do not correlate with audiometric changes,16 emphasizing the importance of reliable analysis of imaging to determine progression of tumors. Agrawal et al recently identified tumor growth as the single most influential factor in alteration of treatment strategy,3 further highlighting the impact of accurately identifying growing tumors.

Methods of accurately assessing VS tumor burden and growth have been widely evaluated. The most commonly employed method in clinical practice consists of following one or more linear measurements of the tumor in serial imaging,1 and much of the literature relies on this method of analysis, frequently using a single maximum linear diameter to assess tumor stability.1-3 In recent years, however, multiple authors have identified the limitations of linear measurements in the assessment of VS,4,5,15 which can assume complex three-dimensional structures that are not fully accounted with linear measures.

Segmented volumetric analysis represents a highly accurate method for assessment of VS volume and has been widely evaluated in the postradiosurgery7-9 and NF-2 populations,6 with fewer examinations focusing solely on sporadic vestibular schwannomas.10,15,16 Multiple methods of segmented volumetric analysis exist, ranging from manual outlining of individual tumor slices with calculation of slice area and multiplying slice area by thickness4 to fully computerized methods using various algorithms,10,15,16 with each method demonstrating significant increases in correlation to actual tumor volume when compared to various methods of tumor volume estimation using linear dimensions.4,6,16 Additional benefits of volumetric assessment include elimination of effects of slice thickness and patient repositioning from scan to scan, which can impact accuracy of linear measurements.16

The present study compares semiautomated segmented conformal volumetric analysis to the use of maximum linear dimensions and orthogonal analysis for estimation of tumor burden and progression. While previous authors have noted underestimation of tumor burden with segmented volumetric estimates derived from linear measurements with small tumors and overestimation with larger tumors,5,6 our study found consistent overestimation of tumor volume with linear measurements compared to segmented volumetric analysis despite the relatively small average size of tumors in the study (Figure 3). This could be attributed to the specific methods of volume estimation (MLD and OA), as these assume a cubic shape of VS rather than the more commonly accepted ellipsoid configuration or average of...
multiple linear dimensions, but Harris utilized MLD$^3$ and identified underestimation of tumor volume with linear estimation.\(^6\) Another potential contributing factor in this overestimation is the inclusion of the intracanalicular portion in tumor length measurement, which was included in both linear and volumetric measurements to accurately represent actual tumor burden.

The accurate identification of progression of VS is the ultimate goal of serial MRI in the wait and scan policy. Authors have used a change of 1 to 3 mm/year or 20% change as benchmarks for linear measurements,\(^1-3,14\) but various parameters have been proposed to define tumor progression in segmented volumetric analysis, ranging from 15% to 73% change in volume.\(^5,6,13,15\) Using the most conservative of these benchmarks, the present investigation identified progression by SVA in 75% more patients than with any other method, a point with the potential for significant clinical implications on management decisions.

The present investigation provides further support to the growing body of literature supporting a paradigm shift in the manner in which VS are assessed and followed, accounting for changes in the complex three-dimensional anatomy of VS where linear measurements cannot. While orthogonal analysis using maximum dimensions in 3 planes does represent an improved estimate of tumor volume and change over time compared with MLD$^3$, orthogonal analysis fell short in identifying progression of tumor with the same frequency as MLD or MLD$^3$, likely secondary to the complex anatomy of the

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**Figure 4.** Comparison of segmented volumetric analysis (SVA), orthogonal analysis (OA), maximal linear diameter (MLD), and MLD cubed (MLD$^3$) assessments of vestibular schwannoma change. Linear data presented as gross percentage change and annual percentage change in maximum linear dimension from initial to final MRI. Volumetric and MLD$^3$ data presented as gross percentage change and annual percentage change in tumor volume. *Denotes significant difference from MLD; † denotes significant difference from MLD$^3$.

**Figure 5.** Identification of progression. While segmented volumetric analysis (SVA) identified 7 tumors meeting criteria for progression, orthogonal analysis (OA), maximal linear diameter (MLD), and cubed maximal linear diameter (MLD$^3$) identified only 4 progressing tumors. Progression was defined as >73% increase for volumetric measures (SVA, OA, and MLD$^3$) and >20% for linear measures (MLD).
vestibular schwannoma that cannot be accurately captured simply by linear measurements. This investigation supports the use of segmented volumetric analysis in the conservative management of sporadic vestibular schwannomas as this provides the most accurate approximation of tumor volume and allows for more reliable identification of progression.

This investigation is not without its limitations. The small sample size and retrospective nature reflect the difficulties of long-term longitudinal imaging follow-up of a sample of patients from a large geographic area who frequently obtain imaging at outside institutions with nonstandardized MRI sequences. Variations in MRI slice thickness and patient position could also be considered weaknesses of the present investigation, but Luppino et al’s recent work identifies no impact of slice thickness or patient position in volumetric assessment. Additionally, an inherent selection bias for slowly growing tumors is present because of the chosen inclusion criteria. Despite this bias toward a more stable VS population, significant volumetric changes were identified, identifying the potential for this method to change management decisions in this population.

An additional limitation of this retrospective study is the lack of clinical follow-up. It is impossible to know whether estimates of tumor growth using SVA would have changed clinical decisions as these were performed post hoc, but identification of tumor growth is often the impetus to suggest a more active treatment strategy for VS, and tumor growth was identified in 75% more patients using SVA. A prospective analysis comparing SVA and traditional estimates of tumor progression would be better suited to identify whether SVA affects rates of transition from the wait and scan method to either surgical or radiotherapeutic treatment strategies.

Another hurdle that limits the clinical utility of SVA and other computerized volumetric methods of tumor assessment is the time commitment. As discussed by Varughese et al, calculation of MLD or MLD^3 requires less than 1 minute while the most reliable manual segmentation volume estimates can take as long as 15 minutes. The semiautomated segmented volumetric assessment utilized in this study occupies a middle ground, requiring approximately 4 to 7 minutes, depending on the slice thickness and tumor size. We feel this balances the time investment and clinically pertinent information gained. Additionally, these measurements can be made prior to the clinical encounter either by the clinician or radiology technologist, minimizing the impact on workflow. While fully automated methods of tumor volume estimation are less time intensive, these still require input from the user to identify the MRI signal qualities to be isolated and measured and are more dependent on the quality of the MRI images and the isolation of the tumor from surrounding structures of similar MRI signal. While these methods are less time intensive for actual volume estimation, reviewing the computer-generated models for accuracy (ie, correctly outlining the tumor in each axial image and excluding extraneous structures) does require additional time. While a full discussion of the methods of automated volumetric assessment is beyond the scope of this discussion, the authors refer the reader to the work of Vokurka et al for a more detailed review.

Conclusion

Vestibular schwannomas assume complex three-dimensional configurations that are not adequately appreciated by single linear measurements and may not accurately be estimated by rudimentary volume estimates. In this study, linear measurements frequently underestimated true tumor growth compared with semiautomated 3-dimensional conformal volumetric analysis, and volumetric estimates using linear data overestimated tumor volume and could not accurately detect tumor progression. Segmented volumetric analysis provides a more robust tool in assessing true tumor volume, growth rate, and volumetric change for a more accurate reflection of tumor progression compared with maximum linear measurements, which can only estimate growth in 1 plane and MLD^3 which does not account for the complex configuration of VS.

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Author Contributions

Patrick C. Walz, conception, design, data acquisition, revising article for intellectual content, and accepting the final version; Matthew L. Bush, conception and design, analysis and interpretation of data, revising article for intellectual content, and accepting final version; Zachary Robinett, acquisition and analysis of data, drafting the article, and accepting final version; Claudia F. E. Kirsch, conception and design, data acquisition, revising article for intellectual content, and accepting final version; D. Bradley Welling, conception and design, acquisition, analysis, interpretation of data, drafting, revising article, and accepting final version.

Disclosures

Competing interests: Claudia F. E. Kirsch, grant recipient, Adenoid Cystic Carcinoma Foundation and Contributor, Primal Pictures 3D Anatomy.

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References


