Longitudinal Radiographic Outcomes of Vestibular Schwannoma in Single and Fractionated Stereotactic Radiosurgery: A Retrospective Cohort Study

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Abstract

Management of vestibular schwannoma (VS) includes stereotactic radiosurgery (SRS) in single or fractionated treatments. There is a paucity of literature on the three-dimensional (3D) volumetric kinetics and radiological changes following SRS and no consensus on appropriate post-SRS surveillance imaging timeline. This is a retrospective cohort study with institutional review board approval. A total of 55 patients met study criteria. We collected volumetric kinetic data in VS treated with SRS over time using a target volume contouring software. We also tracked radiographic phenomena such as pseudoprogression and necrosis. A secondary objective was to describe our overall treatment success rate and any failures. For all treatments groups, pseudoprogression most typically occurred within 12 months post-SRS, after which tumor volumes on average normalized and then decreased from pretreatment size at the last follow-up. Only two patients required salvage therapy post-SRS and were considered SRS treatment failures. Both patients were in the five-fraction cohort but with a lower biologically equivalent dose. Our study is first to collect 3D volumetric kinetics of VS following single and fractionated SRS in contrast to extrapolations from single and two-dimensional measurements. Our longitudinal data also show initial increases in volume in the first 12 months post-SRS followed by later declines, setting up interesting questions regarding the utility of early posttreatment surveillance imaging in the asymptomatic patient. Finally, we show low rates of treatment failure (3.6%) and show in our cohort that SRS dose de-escalation posed a risk of treatment failure.

Keywords
- vestibular schwannoma
- stereotactic radiosurgery
- fractionation
- volumetric
- pseudoprogression

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Introduction

Vestibular schwannoma (VS) is a benign tumor of cranial nerve VIII. Diagnosed in approximately 1.2 patients per 100,000 each year in the United States, VS is treated with surgery, stereotactic radiosurgery (SRS), or observation.[1] As there are no well-established criteria from large high-quality randomized controlled trials for determining treatments, treatment as well as follow-up imaging is often per physician and patient preference. For instance, there is a significant debate on whether to fractionate SRS for patients electing radiation.[2] The rationale for minimizing normal tissue toxicity by distributing dose over 2 to 5 fractions (multifraction SRS) stems from the radiobiology literature: normal late-responding tissues may facilitate repair processes of sublethal radiation damage in the time between fractions.[3–5] There is also some evidence that rates of hearing preservation and posttreatment complications are improved with multifraction SRS compared with single-fraction SRS.[3,6–8] This is more apparent for larger tumors, where the balance between adequate tumor control and toxicity of native tissue is often easier to attain with multifraction SRS.[3,9–11] Multifraction SRS may be particularly suitable for controlling symptomatic mass effect of large tumors causing brainstem compression.[12]

Following radiosurgery, patients are followed with serial imaging to assess for tumor changes and supplement the clinical examination to evaluate the need for salvage therapy. An optimal imaging interval following radiosurgery has yet to be defined, though a typical schedule consists of imaging at 6, 12, 18, and 24 months postradiosurgery followed by annual scans or symptom-driven scans.[13] While radiosurgery has excellent reported tumor control rates, tumor size has been noted to transiently enlarge after SRS, a phenomenon often called pseudoprogression.[6,14] Depending on imaging characteristics, pseudoprogression often appears 3 to 6 months after treatment and by definition will eventually resolve. However, resolution may require years.[15] The frequency of pseudoprogression and its relationship with single-fraction SRS and multifractionated SRS are poorly understood, posing a significant challenge to the clinician in differentiating pseudoprogression from true tumor progression.[16] Moreover, many studies of pseudoprogression and the natural history of VS report volumetric data obtained by unidimensional techniques, which are then used to extrapolate volume based on spherical mathematical equations. The error associated with extrapolated tumor volumes further increases clinical uncertainty regarding postradiosurgical changes.[16,17]

For a better understanding of pseudoprogression and longitudinal radiological outcomes after radiosurgical treatment of VS, we retrospective studied patients treated at our institution with either single-fraction SRS or multifraction SRS for VS. In this report, we detail the timing, nature, and frequency of postradiosurgical volumetric changes including pseudoprogression with quantitated tumor volumes obtained by three-dimensional (3D) volumetric analyses. We hypothesized that patients receiving multifraction SRS would have a decreased incidence of pseudoprogression and a more robust volumetric change compared with patients receiving single-fraction SRS.

Methods

Patient Population

With institutional review board approval (IRB #180127), we retrospectively evaluated all adult patients treated at our institution with SRS between 1998 and 2016 for VS. Informed consent was waived by the IRB due to the minimal risk of the study. For study inclusion, patients were required to have SRS in one, three, or five fractions for VS. Pretreatment postgadolinium magnetic resonance imaging (MRI) with 2 mm resolution was required as well as postradiosurgical serial imaging with at least 2 years of follow-up. A total of 55 patients met study criteria. For each patient, the electronic medical record was assessed for demographics and clinical information.

Radiosurgical Technique

SRS was delivered using the Novalis TX linear accelerator with Brainlab ExacTrac Localization and iPlan Treatment Planning Software (Varian Medical Systems, Palo Alto, California, United States). The treatment team consisted of a radiation oncologist, neurosurgeon, medical physicist, dosimetrist, and radiation therapist. After patient immobilization using a nonrigid thermoplastic mask with stereotactic head frame, simulation head computed tomography (CT) was obtained in 1.5-mm-thick serial axial slices and fused to a recent thin-slice T1-weighted MRI of the brain and internal auditory canals. A customized isocentric 6-MV radiosurgery plan was designed and reviewed at a quality assurance conference. At the time of treatment delivery, kilovoltage (kV) images were obtained with the patient in the treatment position, and isocenter alignment was confirmed by the treating physician. Dose was delivered to planned target volume using either cone or multiload collimation as 1,250 to 1,600 cGy $\times$ one fraction, 700 cGy $\times$ three fractions, or 450 to 550 cGy $\times$ five fractions based on tumor size, potential for hearing preservation, institutional experience, standard of care during treatment study dates, and physician preference.[18–20] At our institution, larger tumors are typically treated with fractionated regimens since larger tumors treated with single-fraction SRS are associated with higher rates of toxicity, and their fractionation mitigates the potential risk of edema and brainstem compression.[21,22] Fractions were delivered on consecutive days.

Study Outcomes

Longitudinal tumor volumes were obtained at the time of SRS planning and when available at follow-up of 6, 12, 24, and 36 months post-SRS, as well from any available additional annual imaging. T1 postcontrast thin-slice (1 mm) MRI was the preferred imaging method to establish tumor volume. If T1 postcontrast thin-slice MRI were unavailable, steady-state gradient thin-slice sequences were used to calculate tumor volume. Tumor volume was determined

using MIM software (MIM Software Inc., Cleveland, Ohio, United States) to contour the entire lesion volume according to standard VS contouring guidelines. Tumor volume was compared serially and between fraction groups using the following formula:

$$\%\Delta(T) = \frac{T_i - T_0}{T_0} * 100\%$$

In the preceding equation, T_0 was the pretreatment tumor volume in cm^3 and T_i was the tumor volume in cm^3 at a specified follow-up. This term was used to account for any differences in baseline volume between groups. Additionally, expressing relative, rather than absolute, change in tumor volume allowed each tumor to serve as its own control, further reducing bias in volumetric comparison. Treatment failure was defined as any patient who required salvage therapy with re-irradiation or surgery. Pseudoprogression was defined as any interval increase in tumor volume that later normalized to or shrank below pretreatment size. Necrosis related to treatment effect (as opposed to radionecrosis) was defined by standard radiological review notable for central hypointensity on T1 postcontrast imaging.[23]

Statistical Analysis

Categorical characteristics were described with the absolute number and relative percentage. Continuous variables were described as the mean and standard deviations (SDs). The Shapiro–Wilk test was performed to assess for a normal distribution of the data. Analysis of variance (ANOVA) was used to compare the differences between continuous variables. When the expected frequencies of categorical variables were noted to be less than 5, Fisher's exact test was performed. Likewise, if the expected frequencies were greater than 5, a chi-square test was used to compare categorical variables. Descriptive graphs were generated, showing the mean and SD of the percent changes in the tumors at various time points, from 6 to 60 months, after therapy. Kaplan-Meier curves were generated to demonstrate the relative difference in the three treatment arms in terms of time to radiologic volume increase by 25%. Log-rank test was used to compare curves in this instance. All tests were two-sided, with a p-value of 0.05 or less being acceptable to reject the null hypothesis that there is no association between the treatment groups. Hazard ratios (HRs) were calculated using a Cox proportional hazards model. All data and graphs were analyzed using R software version 3.5.0 (R project, Vienna, Austria).

Results

The pretreatment clinicopathological characteristics of the patients include for study ($n = 55$) are summarized in ►**Table 1**. Most notably, there was a significant difference in baseline tumor volume between the treatment groups. The five-fraction treatment group had a median tumor volume of 2.13 cm^3 (range: 0.07–6.19 cm^3) compared with a median tumor volume of 1.42 cm^3 (range: 0.39–9.84 cm^3) and 0.745 cm^3 (range: 0.12–3.83 cm^3) in the three-fraction and single-fraction group, respectively ($p = 0.03$; ANOVA). The treatment groups otherwise had no significant clinicopathological baseline differences. Median follow-up was 546 days in the single-fraction group, 1,062 days in the three-fraction group, and 1,139 days in the five-fraction group.

Pseudoprogression

The frequency of pseudoprogression tended to increase in the five-fraction group ($n = 11$; 35%) versus the three-fraction group ($n = 3$; 25%) and the single-fraction group ($n = 3$; 25%) but did not show statistical differences ($p = 0.24$). For all treatment groups, pseudoprogression most typically occurred within 12 months post-SRS, after which tumor volumes on average normalized and then decreased from pretreatment size (►**Fig. 1**). This post-SRS course trend was also observed independently for each treatment group (►**Fig. 2**).

Volumetric Changes

At the time of the last follow-up, tumor volume decreased in single-fraction group (mean %() = –12.5%; SD: 65%), decreased in the three-fraction group (mean %(T) = –2.7%; SD: 49.8%), and increased in the five-fraction group (mean %(T) = 4.7%; SD: 68%) (►**Table 2**). Of note, follow-up volumetric data were not sufficiently available beyond 24 months post-SRS for the single-fraction or three-fraction group but were available for the five-fraction group (►**Fig. 2**). No significant differences in %() were found between the treatment groups on ANOVA ($p = 0.42$), although within each

Table 1 Patient pretreatment clinicopathological characteristics

Variable	One fraction, $N = 12$	Three fractions, $N = 12$	Five fractions, $N = 31$	p-Value
Age	74 (14.5)	58.5 (17.5)	65 (18.5)	0.2
Dose (cGy)	1,250 (37.5)	700 (0)	450 (50)	0.12
Female sex	6 (50)	8 (66.6)	20 (64.5)	0.62
Baseline tumor size (cm^3)	0.745 (0.9)	1.42 (2.36)	2.13 (3.19)	**0.03**
Pre-RT surgery, n (%)	0	1 (8.3)	5 (16.1)	0.29
Baseline necrosis (%)	3 (25)	6 (50)	16 (51.6)	0.27

Abbreviation: RT, radiotherapy.
Note: p-value significance is in bold.

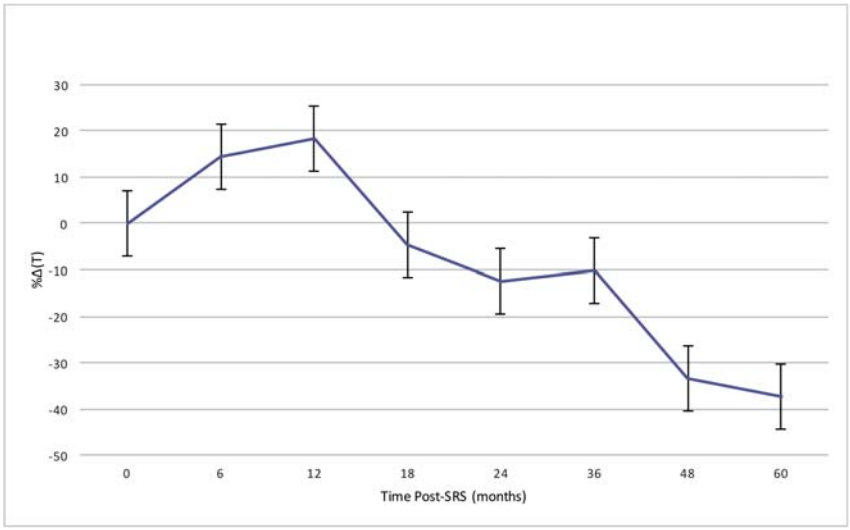

Fig. 1 Volumetric change over time for all treatment groups. SRS, stereotactic radiosurgery.

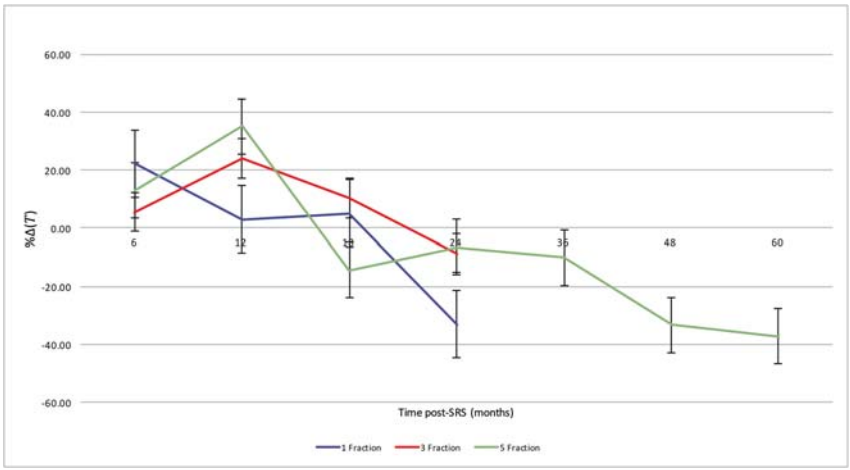

Fig. 2 Volumetric change over time after stereotactic radiosurgery (SRS) by fractionation scheme.

Table 2 Study outcomes by fraction scheme

End point	One fraction	Three fractions	Five fractions	*p*-Value
Pseudoprogression, *n* (%)	3 (25%)	3 (25%)	11 (35%)	0.24
Salvage therapy, *n* (%)	0(0)	0 (0)	2 (6.5%)	0.44
Necrosis at the last follow-up, *n* (%)	7 (58%)	6 (50%)	20 (65%)	0.67
%(*T*) at last the follow-up compared with baseline, mean % (SD)	−12.5 (65)	−2.7 (49)	4.7(68)	0.42

treatment group, volumetric data varied widely. To better delineate between subclinical continuous volumetric change and a clinically significant volume increase, we modeled the probability of %() exceeding or equaling 25% post-SRS using the Kaplan–Meier curves (►**Fig. 3**). No significant differences in time to %() $\geq$ 25% were detected between the treatment groups ($p = 0.28$; log-rank test).

Necrosis

Necrosis at the last follow-up was 7/12 (58%) in the single-fraction treatment group, 6/12 (50%) in the three-fraction group, and 20/31 (65%) in the five-fraction group ($p = 0.67$). Having necrosis at the last follow-up was twice as likely (HR: 2.1; 95% confidence interval: 0.71–6.2) to be associated with a volumetric increase by 25% at the last follow-up ($p = 0.18$; Cox regression).

Salvage Therapy

Only two patients required salvage therapy post-SRS and were considered SRS treatment failures ($n = 2$, 3.6%) (►**Table 2**). Both patients were treated with five fractions, and no patients in the study treated with one or three

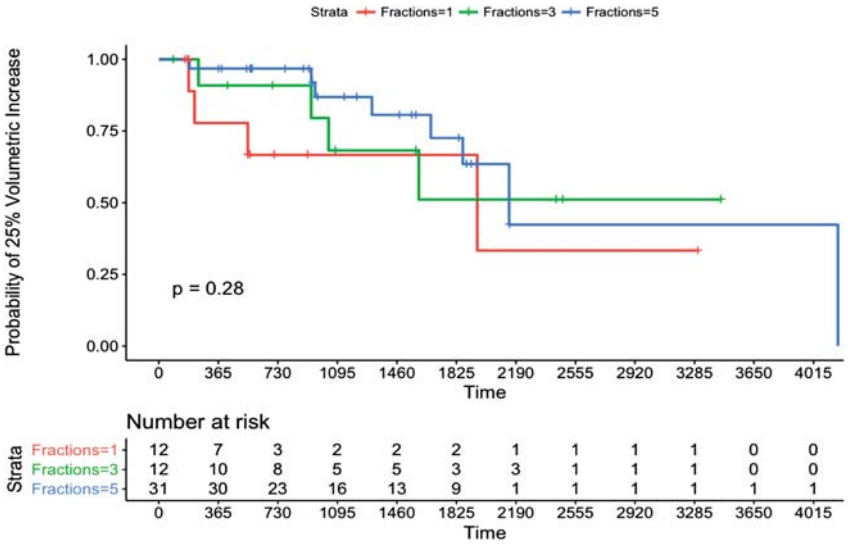

Fig. 3 Kaplan–Meier curve demonstrating time to %() $\geq$ 25% for each treatment group.

fractions required post-SRS therapy ($p = 0.42$; Fischer's exact test).

The first patient initially elected serial observation until radiographic progression to a volume of 4.77 cm^3, which was treated with 450 cGy $\times$ five fractions. After SRS, his tumor grew to 4.98 cm^3 at 3 months and 6.51 cm^3 at 6 months before his next scan at 18 months revealed a tumor volume of 2.78 cm^3. At 24 months post-SRS, his lesion was noted to have increased by 51% to a volume of 4.20 cm^3. He was asymptomatic other than pre-SRS hearing loss. Given the interval increase in his tumor now 30 months after initial SRS, he elected for repeat SRS with 1,250 cGy $\times$ one fraction. He achieved a 3-month-interval decrease in tumor volume to 3.94 cm^3, though he experienced an ipsilateral peripheral facial nerve palsy associated with repeat SRS at the time of the last follow-up.

The second patient originally presented for SRS after recurrence to 2.27 cm^3 following subtotal resection and was treated with 450 cGy $\times$ five fractions. Her tumor volume was 2.91 cm^3 at 3 months, 3.95 cm^3 at 9 months, 4.93 cm^3 at 18 months, and 7.62 cm^3 at 31 months. Due to an interval enlargement of 55%, multidisciplinary tumor board concluded that this radiological progression at 31 months post-SRS was true tumor progression, and she underwent repeat resection without recurrence at last known follow-up.

Discussion

Here we report our institutional experience in treating VS with SRS in 55 patients. We find that the volumetric response to SRS displays noteworthy heterogeneity even within identical fractionation groups. In 25 to 35% of patients, we observe interval enlargement within the first-year post-SRS followed by volume decline consistent with pseudoprogression. Earlier studies of pseudoprogression, such as the report by Flickinger et al, demonstrate pseudoprogression rates of less than 2%, whereas more recent groups have reported rates up to 50%, though imaging varied among these studies.[16,24,25] Our definition of pseudoprogression, as a transient 3D volumetric increase, is more sensitive compared with pseudoprogression defined as planar growth in earlier studies and is closer to rates reported in more contemporary studies.

We do not observe any statistical differences in study outcomes between fractionation schemes. Each treatment group demonstrates on average tumor volumes at the last follow-up close to pretreatment values. The primary study outcomes—pseudoprogression, salvage therapy, necrosis, and volumetric change at the last follow-up—were statistically indistinguishable between fractionation schemes, and we are therefore unable to reject the null hypothesis. Additionally, our study was not powered for noninferiority; therefore, we do not conclude that outcomes are equivalent between fraction groups either. However, there does appear to be a trend toward an association between necrosis and probability of increased volume of at least 25% at the last follow-up, which is not surprising. We suspect that treatment-induced necrosis contributes to this increase in a subset of patients.

Consistent with another volumetric report, we do not find a relationship between pseudoprogression, and clinical status or the need for salvage therapy.[16] If this initial interval growth does not correlate with the need for salvage therapy, and our kinetic data shows volumes generally increase and then decline at 12 to 18 months, then clinical utility of follow-up MRI surveillance within the first 12 months may be currently overstated. As it is well-documented that interval enlargement due to central necrosis is difficult to distinguish radiologically from tumor progression, patients appearing to have progression on imaging early after SRS may unnecessarily undergo intensive salvage therapies such as re-irradiation or craniotomy.[23] Therefore, the risks, utility, and costs of routine surveillance imaging before 12 months in the asymptomatic patient may be currently overutilized.

Notably, although tumor volumes at the last follow-up were not statistically different to pretreatment baseline, we observed only two treatment failures, defined by the need for

re-irradiation or surgery after SRS, and we have illustrated in our study the probability over time of developing volumetric enlargement of 25% or greater. Treated tumors found to be at pretreatment volumes are not necessarily failed treatments because, as we show in this report, their proliferative activity has been sterilized by radiation, terminating the natural history of untreated, unabated growth. From our institution's clinical experience, tumors we have noted to develop central necrosis tend to initially expand and then eventually collapse inward as necrotic core debris is likely cleared. Based on this, we attempted to correlate central necrosis with volumetric expansion. We find a strong, but insignificant, trend toward this relationship, suggesting that central necrosis in the setting of volumetric expansion may be indicative of pseudoprogression rather than true progression and should be interpreted cautiously. However, to fully appreciate this process, a longer period of follow-up would be required than reported here.

The range of doses we used to treat patients in the five fraction cohort were 450 to 550 cGy $\times$ five fractions based on prospective data.[18] Both patients in our study who failed treatment received a lower biologically equivalent dose (450 cGy $\times$ 5 as opposed to a more standard regimen of 500 cGy $\times$ 5), suggesting that perhaps the lower dose is insufficient to neutralize these lesions.[13,26] Importantly, the rationale for reduced dose was to decrease the risk of acute and long-term toxicities. Several reports have described radiation-induced malignancy, including sarcoma, in the cerebellopontine angle after treatment of VS.[27–30] In our study, one patient treated with 700 cGy $\times$ three fractions developed an ipsilateral high-grade sarcoma in the cerebellopontine angle 15 years after SRS for VS. Most likely radiation-induced, this patient's iatrogenic malignancy further underscores the need to strongly weigh nonmaleficence in treatment decisions regarding benign disease such as VS versus the need for local control.

Importantly, in this retrospective cohort study, patients were not randomized to fractionation schemes. The number of fractions was chosen in part for each patient based on presenting tumor size, and larger tumors were significantly more likely to receive a greater number of fractions. While the rationale for treating larger tumors with a larger number of fractions is evidence-based, this nonrandom covariate skews retrospective volumetric analysis to some extent, raising a question of whether statistical comparisons between fractionation schemes are appropriate.[3,9–11] To minimize this bias and avoid overperformance in the multi-fraction groups, we normalized our volumetric analysis to baseline values by using relative change in volume over time instead of an absolute change in volume over time.

Margin tumor dose for single-fraction SRS in our study ranged from 12 to 16.5 Gy. Only three patients in the single-fraction arm received margin dose above 12.5 Gy (14, 15, and 16 Gy, respectively), and each of these patients was treated at the beginning of the study period. The rationale for margin dose greater 13 Gy for these three patients was based on evidence in the literature on gamma knife, which showed excellent local control. For example, Flickinger et al demonstrated 4-year actuarial tumor control rates of 89.2 $\pm$ 6% with minimum tumor doses from 12 to 20 Gy (median: 17).[24] This was further substantiated by a 1998 report in the New England Journal by Kondziolka et al.[31] In this study, tumor margin dose was initially 18 to 20 Gy, but was decreased to 16 to 18 Gy and then further to 14 to 16 Gy to preserve cranial nerve function. Excellent local control was still maintained even with this dose decrease, and this served in large part as the basis for delivering single-fraction SRS at the beginning of our study period with 14 to 16 Gy.[32] After additional data were published on the utility of 12 to 13 Gy, subsequent patients were treated with a 12 to 12.5 Gy $\times$ one fraction regimen.[33]

Follow-up imaging rates for the single- and three-fraction treatment groups were low after 24 months, and this led us to exclude these groups from analysis after 24 months. Loss to follow-up is a general concern for investigations into the treatment of benign diseases such as VS, both because patients may not elect to follow up or may not be required to follow up after being deemed as having stable disease. Additionally, in our study, patients treated with one or three fractions had significantly smaller tumor volumes before treatment, and this likely influenced their lack of radiological follow-up beyond 24 months.

While the strengths of this study include the first 3D-based volumetric analysis using a volume contouring software for accurate measurements of VS kinetics over time in different SRS fractionation regimens, there are several limitations to this study worthy of mention. First, there are inherent limitations in all retrospective studies including obtaining complete datasets of all theoretically possible data points, which we did account for later by using a Kaplan–Meier estimator to reference results relative to loss of follow-up data points. Within the first 24 months of follow-up, there was theoretically a total of 220 possible imaging data points if imaging was performed at 6, 12, 18, and 24 months. In total, 101 images and volumes were contoured, though the frequency of data points was even among the groups. In the single-fraction group, 22 MRIs were available out of 48 theoretically possible MRIs (46%); in the three-fraction group, 22 MRIs were used for volumetric contouring out of a 48 possible MRIs (44%); in the five-fraction group, 48 MRIs were available out of 124 possible MRIs (48%). Importantly, patients with a robust treatment response without symptoms may have prematurely ended clinical and radiographic follow-up, thereby creating a bias in our analysis that they would not have failed at some point in time. Furthermore, lack of daily radiographic images available for the kinetics analysis leads to extrapolation of tumor volumes between images; however, given the slow-growing nature of VS, these extrapolations are most likely reasonable, but variations between when individual patients report for serial images introduce further bias into the model. Finally, our sample size may have underpowered our statistical analysis and led us to make a type II error in our comparison of fractionation schemes. Further investigation is warranted before definitive claims can be made regarding the relationship between volumetric response and SRS fractionation regimen.

Conclusion

We describe a reliable method using volume contouring software to track volumetric kinetics of VS following SRS in one, three, or five fractions. Our findings suggest that VS volume increases in the first 12 months of treatment followed by later decline, suggesting that further investigation is warranted regarding the utility of surveillance imaging in the early posttreatment period as this may overcall progression. Additionally, our data do show very low treatment failure following SRS and a trending association between necrotic changes and small volume increase at the last follow-up, suggesting that small increases at follow-up may not be clinically relevant and may represent radiation-related changes.

Conflict of Interest
None.

Acknowledgments
None.

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