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Scientific Article

Tufts Medical Center Experience With Long-Term Follow-Up of Vestibular Schwannoma Treated With Gamma Knife Stereotactic Radiosurgery: Novel Finding of Delayed Pseudoprogression

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Abstract

Purpose: Our purpose was to evaluate the long-term outcomes of patients with vestibular schwannoma (VS) treated with Gamma Knife stereotactic radiosurgery (GKSRS) with modern techniques, with attention to posttreatment tumor growth dynamics, dosimetric predictors, and late toxicities.

Methods and Materials: One hundred twelve patients with VS were treated with GKSRS with a median dose of 12.5 Gy to the 50% isodose line treated between 2004 and 2015, with patients followed up to 15 years. Target and organ-at-risk doses were recorded, and tumor diameter/volume, audiologic decline, and trigeminal/facial nerve preservation were tracked from treatment onward.

Results: GKSRS yielded local control of 5, 10, and 15 years at 96.9%, 90.0%, and 87.1% respectively. Pseudoprogression was found in 45%, with a novel pattern detected with peak swelling at 31 months. Pseudoprogression was associated with smaller tumor diameter at treatment and fewer treatment isocenters, but not with the development of any toxicity, nor was it predicted by any dosimetric factor. Median time to hearing loss was 3.4 years with actuarial hearing preservation at 2, 5, and 10 years of 66.5%, 43.1%, and 37.6%, with rate of hearing loss correlating with maximum cochlea and modiolus doses. Trigeminal and facial nerve preservation rates were 92.7% and 97.6%, respectively. Increasing maximum tumor dose was associated with facial paresthesia.

Conclusions: Modern GKSRS is a safe and effective treatment for VS on long-term follow-up, with high levels of facial and trigeminal nerve preservation. A novel pattern of pseudoprogression has been identified suggesting longer imaging follow-up may be

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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needed before initiating salvage in those without symptomatic progression. Several tumor and dosimetric predictors have been suggested for the development of different toxicities, requiring further evaluation.

Introduction

Vestibular schwannomas (VSs) are benign, slow growing neoplasms of the nerve sheath of cranial nerve (CN) VIII.[1] They present with a slight female-to-male predominance, typically in the fifth to sixth decades of life, and are the third-most common benign central nervous system neoplasm.[2] Depending on the clinical scenario VS treatment can consist of conservative management with serial observation,[3] surgery, or radiation, each with its own toxicity profile but all with high rates of local control (LC).[1] Numerous single institution retrospective cohorts have examined the efficacy and adverse outcomes of radiation treatment. Due to differences in duration of follow-up, wide ranges of patient numbers, and differences in definitions of and methodology of recording side effects, few results have been validated or reproduced. This study provides a thorough repository of long-term standardized toxicity and dosimetric analysis to add to the growing literature and to redemonstrate safety and efficacy of Gamma Knife stereotactic radiosurgery (GKSRS) with modern techniques. This is the assessment of our long-term experience of management of VS by GKSRS with a retrospective review of a 15-year database (2004-2019).

Methods and Materials

Patients

The cohort consisted of 112 consecutive patients with VS treated with single fraction GKSRS at Tufts Medical Center (TMC) between January 2004 and March 2015, with data updated a final time in December 2019. After approval by the institutional review board, data from medical records were abstracted: demographic characteristics, tumor status/characteristics, dosimetric data (including tumor dose, organ-at-risk dose, and planning parameters), symptoms before and after treatment (including hearing function and audiometry when available), and facial and trigeminal nerve function.

Treatment

GKSRS is performed at our institution with the Leksell Gamma Knife (Elekta AB, Stockholm, Sweden) Perfexion model, and before 2014, with the Leksell Gamma Knife 4C model. In both systems, patients were immobilized using a Leksell Model G frame-based system and imaged with T1 and T2-weighted magnetic resonance imaging (MRIs) using a 1.5T Philips (Koninklijke Philips N.V., Amsterdam, Netherlands) scanner. Patients were planned based on MRI and physical skull measurements. One patient was planned based on 1-mm thin axial with and without contrast computed tomography imaging using the Sensation16 Siemens (Siemens A.G., Munich, Germany) scanner due to inability to tolerate MRI. All patients were treated with a single fraction ranging between 11 to 15 Gy to the 45% to 67% isodose lines. Cochlea and modiolus dosimetry were monitored, using the as-low-as-reasonably-achievable (ALARA) paradigm in those patients with pretreatment serviceable hearing. Tumor type was recorded per Koos grading.[4] For each plan, the volume of the tumor, the maximal antero-posterior (AP), transverse (TRV), cranial-caudal (CC) dimensions (including any internal auditory canal [IAC] involvement), number of shots, coverage, selectivity, gradient index, prescription, dose to tumor margin, maximum tumor dose, and brain stem dose were recorded using Leksell GammaPlan version 10.1.1. Gamma Knife planning terms have been previously defined.[5] If not already performed at date of service (DOS), the cochlea, modiolus, fifth, seventh, and eighth CNs were contoured only if clearly visualized on T1 and/or T2 sequences. The maximum cochlear, modiolus, fifth, seventh, and eighth CNs and the peripheral CN 5 and 7 doses were recorded posthoc. Maximum dose was defined as dose to <0.01 cc of a given structure. Tumor volume was also calculated posthoc using an ellipsoid formula ($[\pi/6]XD_{AP}XD_{TRV}XD_{CC}$) in cubic millimeters ($mm^3$) as previously described.[6] Tumor measurements were performed before determining tumor outcome or toxicity per patient to avoid measurement bias.

Follow-up and statistical analysis

Patients were followed after treatment at 6-month intervals for the first 1 to 2 years and subsequently every 1 to 2 years once the tumor and symptoms became stable. Hearing and facial nerve testing was performed by the treating neurosurgeon and radiation oncologist and via audiology/otology evaluation when available. Tumor size was measured on all enhanced MRI (including the treatment study) in a standardized manner, in 3 maximal perpendicular dimensions (including any IAC involvement).[7] Tumor growth dynamics were determined only with the ellipsoid volume calculation from DOS and at each follow-up scan. Only

GammaPlan calculated volumes were used for comparison of tumor characteristics between cohorts at DOS. GK failure (GKF) was retrospectively defined as patients who required any form of salvage treatment, at the time of salvage treatment or upon referral to a secondary provider for consideration of salvage. Prospectively, salvage was typically recommended after continued tumor growth and progressive symptoms at least 2 years after DOS or after growth without progressive symptoms of at least 5 years (of which both criteria temporally occurred outside of the accepted timeframe of pseudoprogression). Pseudoprogression was defined as any tumor that experienced a recorded minimum of a 10% volume (mm^3) increase occurring between 2 and 18 months as previously described,[8] followed by either several years of stability or shrinkage. If no imaging data were available after the documented increase in volume, 1 subsequent follow-up documenting absence of GKF was required. Ad hoc comparison of pseudoprogression versus tumors without pseudoprogression was conducted. Hearing function was evaluated by audiograms with ipsilateral percent speech discrimination scoring (%SDS) and Gardner-Robertson (G-R) scoring.[9-11] Subjective facial weakness or twitching was flagged, and House-Brackmann (H-B) scale[12] scoring used. Serviceable hearing was defined as G-R I-II,[13] and facial nerve preservation was defined only as H-B score I. Any mention of subjective facial numbness, tingling, or paresthesia were all recorded as dichotomous yes/no responses. Differences in mean values were tested for significance using the independent 2 tailed *t* test for comparison between 2 groups. The X^2 or Fisher exact test was used where appropriate for categorical data. Cox proportionate hazards models were used to analyze hazard ratios for patient, treatment, and VS characteristics on the occurrence of hearing preservation, facial nerve preservation, and trigeminal nerve preservation. Pearson correlation testing was performed to determine whether there were any relationship between the degree of change of %SDS per month and different tumor and dosimetric parameters. To determine agreement between tumor volumes as determined by the Leksell GammaPlan version 10.1.1 and ellipsoid calculation of volumes at DOS, an intraclass correlation coefficient was calculated using a 2-way mixed mode with absolute agreement, yielding an average measures value at 0.975. All statistical testing used SPSS version 26 (SPSS, Chicago, IL).

Results

Patients

The median age of the 112 patients was 61 years at DOS (range, 21-86), of which 52 were female (46%). Twenty patients had received previous treatment, 19 of whom underwent previous surgical resection and 1 who underwent stereotactic radiation therapy. Most patients had Koos II tumors at 37% (Table 1).

Local control

Dosimetric parameters for patients who experienced tumor control and failure are displayed (Table 1). Of the 112 patients, 9 experienced GKF, yielding an overall 92% LC rate. Six failures were salvaged with surgical excision with pathologic confirmation of schwannoma, 1 underwent repeat GKSRS, and 2 were referred for salvage and subsequently declined intervention. There was no statistically significant differences for any of the patient, tumor, or dosimetric parameters recorded between GKFs and non-GKFs, including age at DOS, presence of neurofibromatosis type 2 (NF2), tumor peripheral or maximum doses, tumor coverage, or number of isocenters. Due to the change in treatment machine, GKFs are categorized by before and after 2014, with all failures having occurred before 2014. Median time to GKF was 57 months but ranged from 29 to 123 months. Progression-free survival and LC at 1, 2, 5, and 10 years was 100%, 99.1%, 93.8%, and 85.4%, and 100%, 100%, 96.9%, and 90.0% respectively (Fig 1A,B). No patient developed a radiation-associated neoplasm during the follow-up period.

Pseudoprogression and tumor volume dynamics

After review of tumor dynamics using ellipsoid volumetric calculations, a total of 74 patients had sufficient radiographic data for analysis. Twenty-seven (35.1%) met criterion for pseudoprogression (distinguished here as "type 1"), with more classical characteristics with a median peak time at 6 months[8,14] (Fig. 2A and 3A). Forty-one patients (55.4%) experienced tumor regression without evidence of swelling (Fig 2B). A second pattern of pseudoprogression emerged meeting the definition of neither type 1 nor GKF: "type 2," with a peak volume increase occurring at a median of 31 months with total range of swelling persisting for 31 to 73 months followed by regression (Fig. 2C and 3B, and Table 2). Representative radiographic follow-up and tumor dynamics for GKF are provided for comparison (Fig 2D). Upon comparison of type 1 tumors and those without pseudoprogression, type 1 had a significantly smaller AP dimension at 9.32 mm versus 12.32 mm (P = .007) and TRV dimension at 14.2 mm versus 17.2 mm (P = .032), with fewer number of isocenters (9.5 vs 13.2, P = .042). There were no significant differences in terms of gender, laterality, prior treatment, NF2 status, Koos grade, tumor volume, or any other dosimetric parameter recorded (including coverage, tumor maximum/minimum, or brain stem maximum

Table 1 Baseline patient, tumor, and dosimetric characteristics of 112 patients treated with GKSRS

Parameter	Patients with failure (n = 9)	Patients with control (n = 103)
Age at DOS (years), mean (SD)	54 (10.8)	59 (12)
Sex, no. of patients (%)		
Female	5 (56)	47 (45.6)
Male	4 (44)	56 (54.4)
NF-2	0	3 (2.9)
Cystic, no. of patients (%)	1 (11)	10 (9.7)
Laterality, no. of patients (%)		
Left	4 (44)	44 (42.7)
Right	5 (56)	59 (57.3)
Previous treatment*	1 (11)	19 (18.4)*
Koos class, no. of patients (%)		
A	2 (22.2)	20 (19.4)
B	4 (44.4)	43 (41.7)
C	2 (22.2)	27 (26.2)
D	1 (11.1)	13 (12.6)
Volume (mm^3), mean (SD)	1393 (1897.3)	1524 (1908.7)
Max AP diameter (mm), mean (SD)	10.8 (3.9)	11.3 (5.2)
Max TRV (mm), mean (SD)	18.1 (5.7)	15.8 (5.9)
Max CC (mm), mean (SD)	10.6 (5.0)	11.5 (5.6)
Coverage, mean (SD)	0.93 (0.10)	0.94 (0.15)
Selectivity, mean (SD)	0.64 (0.09)	0.65 (0.16)
Gradient index, mean (SD)†	3.1 (0.25)	3.0 (0.34)
Dose to tumor margin (Gy), mean (SD)	10.5 (2.7)	11.1 (2.5)
Max tumor dose (Gy), mean (SD)	23.8 (1.6)	25 (1.6)
No. of shots, mean (SD)	9.2 (4.6)	11.5 (7.8)
Date of GK treatment, no. of patients (% of total)		
Before 2014	9 (100)	92 (89.3)
After 2014	0 (0)	11 (10.7)
Ipsilateral toxicity at treatment, no. of patients (%)		
H-B I	9 (100)	86 (83.5)
H-B II	0	5 (4.9)
H-B III	0	3 (2.9)
H-B IV	0	3 (2.9)
H-B V	0	6 (5.8)
H-B VI	0	0
G-R I-II	5 (55.6)	54 (52.4)
G-R III-V	4 (44.4)	49 (47.6)
Paresthesia	2 (22.2)	12 (11.7)

Abbreviations: AP = antero-posterior; CC = cranial-caudal; DOS = date of service; GK = Gamma Knife; GKSRS = Gamma Knife stereotactic radiosurgery; G-R = Gardner-Robertson; H-B = House-Brackmann; NF-2 = neurofibromatosis type 2; SD = standard deviation; SRT = stereotactic radiation treatment; TRV = transverse.

* All with previous surgical resection except for 1 patient with prior SRT.

† Ninety total patients with baseline gradient indices available.

doses). There was no increased likelihood of developing transient toxicity or loss of serviceable hearing in those who experienced pseudoprogression on X^2/Fisher's exact testing, all with $P > .05$.

Hearing preservation

At baseline, 53% of all patients were recorded as having serviceable hearing. Of 53 patients with at least 1 year of toxicity specific follow-up, 21 patients (40%) maintained serviceable hearing at last follow-up, with a median time to loss of serviceable hearing at 19 months (ranging from 3-158 months). Only 2 patients experienced transient worsening of hearing from G-R II to III, returning to baseline at last follow-up. Only 1 patient experienced improved hearing by last follow-up (from G-R III to II). All other patients maintained pretreatment G-R baseline or worsened. Actuarial median time to loss of serviceable hearing was 3.4 years (Fig 4A), with no significant predictors for hearing loss on univariate analysis (UVA) of age at DOS, tumor size in the TRV or CC dimension, maximum/marginal tumor doses, or

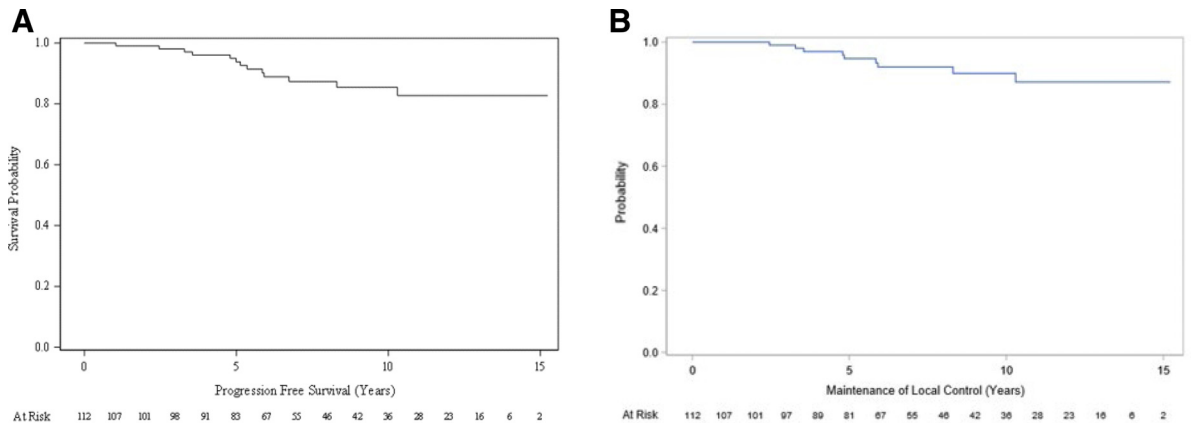

Figure 1 (A) Progression free survival of 112 vestibular schwannomas (VSs) treated with Gamma Knife stereotactic radiosurgery (GKSRS). (B) Local control of 112 VSs treated with GKSRS.

cochlear/modiolus maximum doses. There was a trend toward more advanced age at DOS (62 vs 58, $P = .098$) and more Koos grade I (35 vs 14%, $P = .069$) in those who lost serviceable hearing. There were no significant differences in terms of any other tumor characteristics or dosimetric parameters (including marginal and maximal tumor doses and maximal cochlear, modiolus, and CN VIII doses). Of those patients with available audiometry testing just before treatment and at least 1 measurement after treatment (n = 28), there was a moderate correlation between the rate of change of speech discrimination (%SDS/mo) and the cochlea and modiolus maximum doses at 0.49 ($P = .015$) and 0.5 ($P = .012$), respectively. There was little to no correlation with the age at DOS (0.009, $P > .05$) or with any other tumor characteristic or dosimetric parameter.

Trigeminal nerve preservation

At DOS, 12.5% reported some degree of ipsilateral facial paresthesia. Of those with at least 1 year of toxicity-specific follow-up without initial paresthesia, there was a 92.7% (76/82) rate of trigeminal nerve preservation. Of those starting with some form of paresthesia (n = 7), the median time to recovery was 18 months. The median time to development of any reported paresthesia was 7 months. Actuarial median time to facial paresthesia was not reached (Fig 4B). There were no significant predictors of paresthesia on UVA of 2-dimensional tumor dimensions, maximum CN V dose, or peripheral tumor dose. There was a trend for increased hazard ratio for maximum tumor dose at 1.22 (95% confidence interval, 0.95-1.56), with a mean max tumor dose at 25.5 versus 24.7 Gy ($P = .075$). There was a significantly lower selectivity index in those who never developed paresthesia at 0.62 versus 0.70 ($P = .049$). There was no significant difference in other tumor characteristics or dosimetric parameters (including peripheral tumor dose or CN V maximum/peripheral doses).

Facial nerve preservation

Eighty-eight percent of patients were without any form of facial weakness at DOS. Although no patient reported any hemifacial spasm (HFS) at DOS, 8 patients developed this side effect; none reported it at last follow-up. Of those with HFS, 4 patients did not develop associated subjective or objective facial weakness, 2 developed *transient* facial weakness, 1 developed facial weakness at last follow-up, and 1 patient started with facial weakness at DOS that subsequently resolved at last follow-up. The median time to development of HFS was 8.5 months. Of those with at least 1 year of facial nerve specific follow-up, there was a 97.6% preservation rate. Actuarial median time to development of facial weakness was not reached (Fig 4C). Of 13 patients who started with some form of weakness, 4 later resolved (who had no greater than H-B III at DOS), with the median time to resolution at 6 months. Within these 13 patients, 10 had also undergone previous surgery. (It should be noted that postoperative healing may have occurred as opposed to GKSRS-related resolution.) Of 95 patients with no weakness at treatment, only 2 patients later developed permanent weakness, whereas 5 patients experienced transient facial weakness at a median of 10 months from treatment. Tumor dimensions, peripheral and maximum tumor doses, and maximum CN VII doses did not predict risk of facial weakness on UVA. The only significant difference in tumor characteristics or dosimetric parameters between those with any form of CN VII toxicity versus those with none was a higher average number of isocenters for those without symptoms at 11.4 versus 7.7 ($P = .005$).

Discussion

GKSRS has been used in the treatment of VS for over half a century, and in the modern era provides high levels of long-term LC while improving hearing and CN

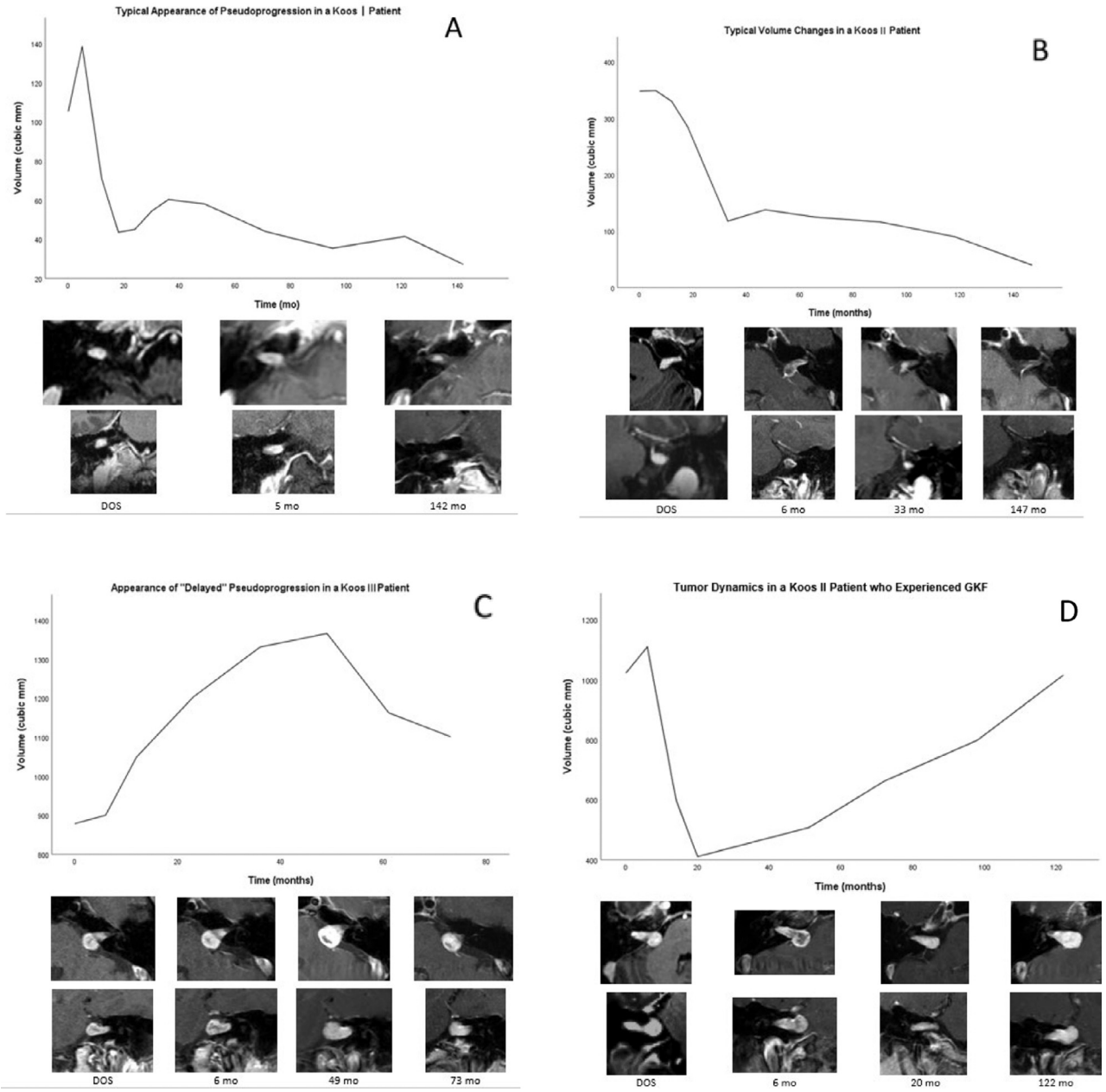

Figure 2 Change in tumor volume (mm^3) over time (mos), with representative axial and coronal T1 postcontrast magnetic resonance imaging (MRI), mid and lower panels respectively. (A) Type 1 pseudoprogression in a Koos I patient who experienced a 30% volume increase with peak time of 5 months, nadir at last follow-up, with imaging at date of service (DOS), 5, and 142 months. (B) Tumor dynamics in a Koos II patient without evidence of pseudoprogression, with imaging at DOS, 6, 33, and 147 months. (C) Type 2 pseudoprogression in a Koos III patient who experienced a 55% volume increase with peak time of 49 months with posttreatment nadir not reached, with imaging at DOS, 6, 49, and 73 months. (D) Tumor dynamics in a Koos II patient with Gamma Knife failure (GKF), with imaging at DOS, 6, 20, and 122 months.

preservation.[10] LC continues to be defined as the need for a second intervention as opposed to radiologic changes,[6,15] with rates of progression-free survival ranging between 92% and 100%.[13] Overall, LC hovers around 95%[15] on systematic review with mean follow-ups of approximately 8 years in tumors <2 cm.[11] These results compare favorably to our experience, with a mean follow-up of 7.9 years and an overall LC of 92% with an average maximum diameter and volume of 1.28 cm and 1.4 cc, respectively, including tumors as large as 3 cm in diameter and 8.7 cc in volume. This study was also consistent with previous cohorts where most failures occur around 4 to 5 years after treatment,[8,13,14,16-18] with late failures being extremely uncommon after 10 years.[18] Although previous studies have identified factors influencing the likelihood of failure, such as tumor volume

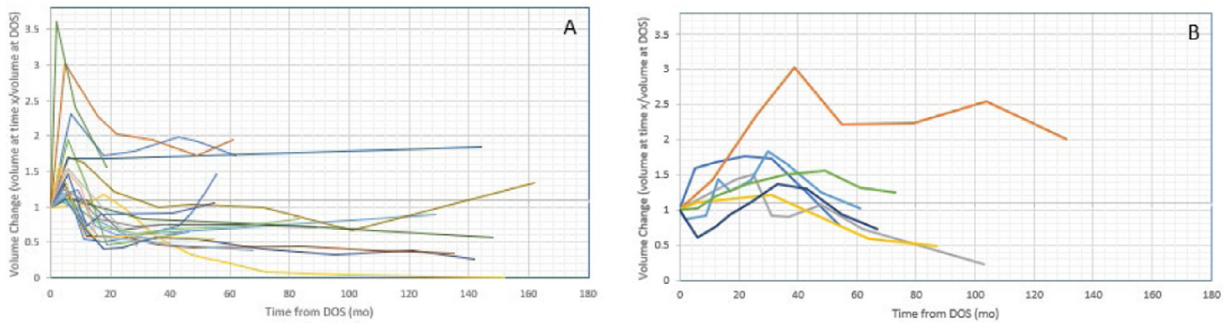

Figure 3 Relative change in tumor volume (volume at time of measurement/volume at date of service [DOS]) versus time (months), with the x-axis set at a 10% volume increase. (A) Type 1 pseudoprogression tumor dynamics. (B) Type 2 pseudoprogression tumor dynamics.

and type,[17] marginal dose, prior treatment, and gender,[18] no such associations were detected in this review. Conversely, lack of influence of NF-2, patient age, prior treatment, or tumor size on LC[19] has also been shown. Despite an increasing number of long-term follow-up studies within the literature, these results highlight continued conflicting evidence, with analyses limited to retrospective reviews, each with different methods for measuring and defining tumor characteristics, dosimetric parameters, and treatment-related outcomes.

Similarly, standardization in tracking tumor growth dynamics in the identification of pseudoprogression in cohorts of VS is lacking, making comparison between studies challenging. Some use linear measurements with definitions requiring growth beyond 2 to 3 mm,[14,17,20] while others have used volumetry with growth thresholds >10%[6,21,22] or >20%.[8,14] Pseudoprogression has thus been fundamentally defined as a transient increase in size followed by stability or regression.[11,22] "Transient" frequently remains undefined. Pseudoprogression has been identified in 5% to 72% of cohorts, occurring between 5 to 16 months after treatment.[8,13,14,20,22-24] In the TMC experience, pseudoprogression was recorded at comparable rates; however, we identified 2 distinct patterns of pseudoprogression (Table 2, Fig. 2A,C and 3). Type 1 conforms to an earlier peak with a relatively short duration of swelling, whereas the type 2 peak occurs later and for a longer duration. Unfortunately, a small sample size precluded further comparative analyses. Subjectively, the radiographic appearances of swelling of type 1, type 2, and GKFs are similar (Fig 2). Figure 3 scales all Koos types so that the patterns of growth between Type 1 and 2 pseudoprogression can be subjectively compared. The eventual decrease in size coupled with asymptomatic radiographic swelling as observed in type 2 pseudoprogression is the major distinguisher compared with a continuous growth pattern (± symptom development) as in those with GKF (Fig. 2C,D and 3B). There is a great deal of heterogeneity within the type 2 pseudoprogression population. Further analysis of a larger sample is required to investigate other elements to help clinicians understand the nature of type 2 pseudoprogression and to aid in discrimination from potential GKFs. This is the first description of this form of pseudoprogression to the knowledge of the authors. Pseudoprogression has been predicted by larger tumor volume,[8,20] previous surgery, female gender, or higher dose.[8,17,20,24,25] Conversely, our analysis identified that *smaller* tumor dimension and fewer isocenters have played some role. There was no significant difference in tumor volume, gender, or previous surgery. Fewer number of isocenters with no difference in selectivity, coverage, or tumor doses would suggest the difference in pseudoprogression may be more intrinsically related to tumor size. As all tumors likely experience some degree of treatment-related inflammation,[26,27] the presence of swelling may not be as apparent in larger tumors, as this population would have less available potential growth space (being the IAC), compared with smaller tumors that at baseline occupy a smaller percentage of this space. This hypothesis would be in line with Hayhurst and Zadeh,[22] where they identified a *lower* brain stem maximum dose as a predictor of

Table 2 Pseudoprogression variants and growth dynamic characteristics

Parameter, median (first-third quartile)	Type 1, n = 26	Type 2, n = 7
Volumetric growth factor (peak volume/baseline volume)	1.34 (1.19-1.66)	1.56 (1.44-1.80)
Time to peak volume (mo)	5.5 (4.8-6)	31 (27.5-36)
Duration of swelling (mo)	17 (15-22.3)	55 (51-59.5)
Time of nadir (mo)	29.0 (19.3-64.8)	73 (30-95)

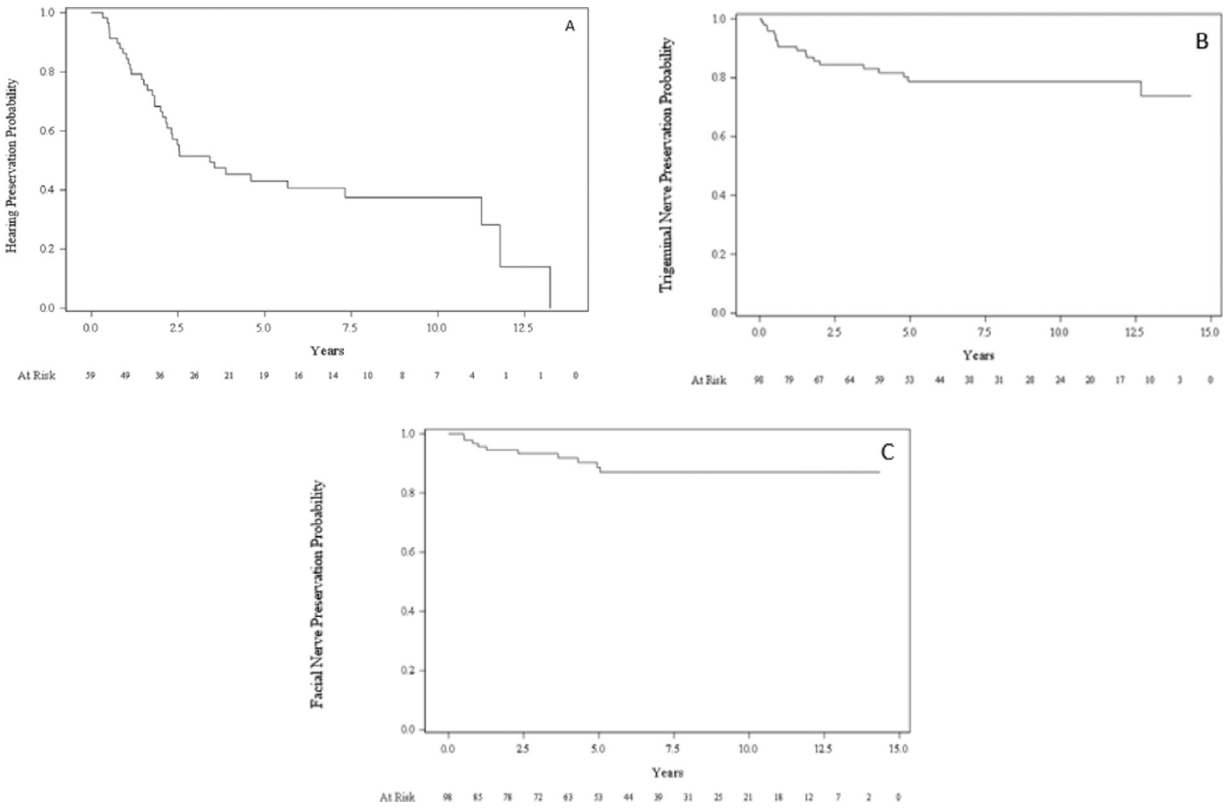

Figure 4 (A) Probability of maintaining Gardner-Robertson (G-R) I-II for 59 at-risk patients. (B) Probability of trigeminal nerve preservation for 98 at-risk patients. (C) Probability of facial nerve preservation for 98 at-risk patients.

pseudoprogression. This could be indicative of a smaller treatment volume given the high conformity indices reported. This contrasts with other hypotheses suggesting swelling is directly related to a radiobiologic process[20,28]; however, there is no evidence to suggest a difference in size or Koos grade belies a distinct biological profile. Regardless of the cause of pseudoprogression, it must be a recognized and defined entity so as to avoid unneeded salvage treatment. The new description of type 2 pseudoprogression would indicate swelling can peak 31 months posttreatment. Although others have conjectured that pseudoprogression may lead to worsening toxicity or treatment failure, we did not find evidence of a link with treatment failure or any hearing decline or other measure of transient toxicity.

With respect to toxicity, quality of life analyses have identified the most important patient-ranked issues as hearing loss and facial nerve dysfunction.[29] Previous reviews identified that dysfunction of CNs and hearing deterioration can be delayed for 2 to 3 years after treatment.[10,15] With longer follow-up, hearing loss can occur due to age-related deficits[29] and in patients with VS undergoing conservative management *without* tumor growth,[13] consistent with other studies of long-term imaging follow-up alone.[3,30] Recent studies suggest hearing preservation rates of 55% to 68% at 2 to 3 years,[16,18,31] 43% to 69% at 4 to 5 years,[18,23,32] with rates at 10 years to about 20% to 23%.[16,33] Actuarial hearing preservation in our evaluation at 2, 5, and 10 years was comparable at 66.5%, 43.1%, and 37.6%, respectively. Besides a nonsignificant trend toward small intracanalicular tumors within the group who lost serviceable hearing, there were no dosimetric trends or predictors. Although larger tumor volume was not more likely to predict hearing loss, a larger number of Koos I found in this group highlights a potential higher risk for tumors within the IAC. The lack of dosimetric findings may be a combination of a relatively small sample size plus a consequence of long-term follow-up and natural disease course. Regardless, there is an abundance of data to indicate a higher risk of hearing loss with higher cochlear and modiolar doses.[34-37] Furthermore, a significant correlation between the rate of hearing loss as measured by %SDS/mo and cochlear and modiolus maximum doses was demonstrated, providing further support for an ALARA paradigm.

With respect to trigeminal and facial nerve toxicities, trigeminal nerve injury was documented at 17% to 33% in the 1990s.[38] With dose de-escalation, modern preservation rates are 92% to 100% depending on the duration of follow-up.[13,15] Facial nerve injury has likewise improved from rates of 17% to 29%,[10,38] now 0% to

11.2%.[11,15] Unlike hearing preservation, these rates do not appear to gradually worsen with time, but rather stabilize. Both trigeminal and facial toxicity have been found to occur on average around 6 to 8.6 months after treatment.[20,39] A distinct facial nerve toxicity, facial twitch, or HFS has been described in 2% to 3.5% of cohorts.[6,14] There appears to be some disagreement in the cause and timing of HFS within the literature; however, the TMC cohort most closely matches that previously described by Norén.[40] HFS in this case did not appear related to the development of subsequent weakness or failure. The rates and timing of traditionally defined neuropathy compare favorably with CN V and VII preservation rates determined from the TMC cohort; actuarial analyses support their durability. Hasegawa et al[18] persistently observed higher rates of trigeminal and facial nerve complications in those patients who received marginal tumor doses greater than 13 Gy. Others have postulated the length of the CN irradiated may be the major predictor of toxicity.[41] Although these dimensions were not recorded in this study, the peripheral doses of CN V and VII were examined and not associated with development of toxicity. Higher selectivity and higher maximum tumor dose were associated with trigeminal neuropathy in our series, whereas maximum CN V dose was not, suggesting a certain volume of the nerve subjected to higher dose may be related. The specific dosimetric cut off remains elusive. A higher average number of isocenters was associated with facial nerve preservation, which remains a point of contention: a larger number of isocenters has been associated with both increased CN preservation[42] and with earlier development of worsening neuropathy.[43] Owing to small numbers of HFS, a dosimetric analysis could not be performed; however, Norén's hypothesis that the complication is part of a dose-response curve within the spectrum of facial weakness is intriguing.[14] Although specific predicting dosimetric factors remain unclear, with modern techniques, fifth and seventh CN preservation rates exceed 90%.

Conclusions

This study contains a long-term descriptive analysis of the most modern patient cohort of patients with VS treated with GKSRS. LC remained excellent, with low levels of trigeminal and facial nerve toxicity. The study has revealed more detail on the nature of pseudoprogression and the patterns of tumor growth after radiosurgery, with evidence of newly identified late transient volume increase. This suggests the need for longer posttreatment surveillance before engaging in potentially erroneous salvage treatment in the absence of symptomatic progression; however, further investigation with a larger sample size is required before any recommendations to change the standard of care. One recommended future avenue for further assessment would be examining volume growth rates *in combination* with change from baseline volume. With a growing database, we plan to report on this in a follow-up analysis. Our review has also provided further elucidation on the typical timing and likelihood of development of different toxicities using modern treatment methods. Based on the lack of significant differences in toxicity outcome with dosimetric factors investigated, there is no current basis for contouring additional organs at risk outside of the current standard of care at this time. Identification of specific dosimetric parameters predicting for toxicity remains elusive and the literature sparse. The analysis also highlights the need for standardization of data recording and collection in terms of dosimetry and toxicity endpoints. With the advent of more advanced treatment and imaging systems, this level of insight should lead to continued excellent LC while continuing to lower the likelihood of incurred toxicity.

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