Long-Term Outcomes of Fractionated Stereotactic Proton Therapy for Vestibular Schwannoma: A Case Series

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Abstract

Purpose: Evaluate clinical outcomes in patients with vestibular schwannoma (VS) treated with fractionated proton therapy (PT) at a single institution.

Materials and Methods: We retrospectively reviewed the medical records of patients treated with fractionated PT for definitive management of VS between November 2007 and December 2013 at our institution. No patient had received prior treatment for VS. Patients received 50.4 Gy in 28 fractions using passively scattered PT. Pretreatment and posttreatment hearing status, tumor dimensions, and cranial nerve V and VII function were evaluated. Hearing status was graded as nonserviceable or serviceable, defined as Gardner-Robertson grade I or II and the ability to use a telephone with the treated ear. Toxicities were prospectively evaluated using Common Terminology Criteria for Adverse Events, version 4.0.

Results: Fourteen patients with 14 lesions (8 men, 6 women) were included in the analysis. Median age at treatment was 60 years (range, 24–74 years). Median clinical follow-up for living patients was 68 months (range, 36–106 months). Mean maximal tumor dimension was 2.1 cm (range, 0.5–3.8 cm). Mean tumor volume was 6.4 cm^3 (range, 0.3–16.0 cm^3). One patient died of unrelated causes 5 months after treatment, and 2 had subsequent surgical resections due to radiographic and/or clinical progression. The actuarial 3-year local control rate was 85%. There were no cranial nerve V or VII injuries. Two of 6 patients (33%) with serviceable hearing at the time of treatment retained serviceable hearing. Three patients (21%) demonstrated radiographic tumor regression on brain magnetic resonance imaging after a median of 26 months (range, 2–113 months). No acute toxicity of grade 3 or above was reported.

Conclusion: Fractionated PT for VS is well tolerated and provides good local control. Improvements in proton delivery techniques and patient selection may enable improved outcomes.

Keywords: acoustic neuroma; proton therapy; radiation oncology

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Introduction

Vestibular schwannoma (VS) is a benign intracranial tumor originating from the Schwann cells surrounding the vestibular portion of cranial nerve VIII with an incidence of about 1

Table 1. Patient demographics and tumor characteristics.

Patient No.	Age	Sex	Race	Laterality	Maximum tumor dimension (cm)	Tumor volume (cm^3)
1	74	M	Black	R	1.6	1.0
2	60	M	White	L	2.8	15.5
3[a]	24	F	Black	L	2.5	2.1
4	33	F	White	L	1.7	0.7
5	54	F	White	R	1.1	0.7
6	61	M	White	R	2.5	5.8
7	54	F	Black	R	1.9	1.1
8	74	F	Asian	R	3.4	16.0
9C	47	M	White	L	2.4	4.9
10	62	M	White	L	1.9	1.0
11	71	M	Asian	R	3.8	11.8
12	41	F	Black	R	1.6	0.9
13	74	M	White	L	0.5	0.3
14	61	M	Black	R	3.0	6.9

Abbreviations: M, male; R, right; L, left; F, female; C, cystic tumor.
[a]Neurofibromatosis type 2.

per 100,000 people [1]. It can occur either sporadically or as part of neurofibromatosis type 2, a syndrome associated with bilateral VSs.

Microsurgery has traditionally been the treatment of choice for VS due to its high rate of local control, but it is associated with an increased risk of facial and/or trigeminal nerve injury [2–4]. Meanwhile, radiation therapy has been used more widely as an alternative treatment for VS since it often achieves a similar local control rate and is more likely to preserve hearing and cranial nerve functions [1]. Radiation therapy can be delivered through several modalities, including stereotactic radiosurgery, which uses a single high-dose fraction, to conventionally fractionated radiotherapy, which uses smaller daily doses typically delivered in 28 to 32 fractions [5–15].

The proximity of typical VS to the critical surrounding structures (eg, the cerebellum, brainstem, cranial nerves) makes conventionally fractionated stereotactic radiotherapy with protons a promising treatment modality since fractionated radiotherapy is known to incur less damage to surrounding normal tissues [16, 17]; in addition, the physical properties of a proton beam allow for more radiation energy to be concentrated on the target, thereby sparing surrounding normal tissues [18, 19]. There have been reports on hypofractionated or stereotactic proton therapy (PT) [9–11] for VS; however, to our knowledge, there is only one outcomes study analyzing conventionally fractionated PT for VS [8]. In the current study, we evaluate outcomes, including disease control and treatment-related toxicity, in patients with VS treated with PT at our institution using a uniform treatment approach.

Patients and Methods

Under institutional review board approval, we retrospectively reviewed the medical records of 14 consecutive patients with 14 lesions treated with fractionated PT between November 2007 and December 2013 at our institution. No lesion received any treatment prior to PT.

Patient Demographics and Disease Characteristics

Demographic information and tumor characteristics for the 14 patients—8 men and 6 women—are detailed in **Table 1**. Six patients had serviceable hearing at the time of radiotherapy treatment. The median age at treatment was 60 years (range, 24–74 years). Eight patients had right-sided lesions while 6 had left-sided lesions. One patient (No. 3) had neurofibromatosis type 2 and bilateral VS. Only the left lesion was included in this study since she received surgery without radiation to the contralateral side. The mean and median maximum tumor diameters were 2.1 and 2.1 cm, respectively (range, 0.5–3.8 cm).

The mean and median tumor volumes were 6.4 and 3.9 cm^3, respectively (range, 0.3–16.0 cm^3). One lesion had a cystic component at the time of treatment.

Radiation Therapy

All patients received 50.4 Gy(RBE) in 28 fractions of 1.8 Gy(RBE)/fraction using passive double-scattered PT. Target volumes included the gross tumor volume with a 5-mm planning target volume (PTV) expansion. For all but 1 patient, no clinical tumor volume (CTV) expansion was used (gross tumor volume [GTV] = CTV). One patient (No. 7) had a treatment volume that included a 3-mm CTV expansion and a 5-mm PTV expansion. Proton plans consisted of 2 or 3 fields avoiding proton fields with an end of range in the brainstem due to an increase in relative biologic effectiveness at the end of range (in the final few millimeters of the spread-out Bragg peak) and potential risk for increased brainstem injury. Individualized brass apertures and Lucite compensators were generated for each patient. Daily orthogonal x-rays based on bony anatomy were used for daily image guidance. For photon comparison plans, volumetric modulated arc therapy plans were generated utilizing 6-MV photons and consisted of 2 to 4 arcs. The target volumes (GTV, CTV, and PTV) used for volumetric modulated arc therapy planning were identical to those used for proton planning. Target coverage (100% of the PTV covered by 95% of prescription dose; $\geq$99% of the GTV covered by the prescription dose) and brainstem dose constraint (maximum dose to 0.1cm^3 $<$ 55 Gy[RBE]) were prioritized as part of both proton and photon treatment planning. Efforts were made to reduce the dose to the cochlea (goal = mean dose $<$36 Gy[RBE]) while maintaining target coverage.[20, 21]

Pretreatment and Follow-Up Evaluation

The pretreatment and follow-up evaluations included clinical and radiographic tumor assessment, hearing evaluation, and cranial nerve examination. The determination of patients' pre-PT and post-PT hearing status was based on audiometry reports and clinical assessment of hearing capability. Hearing status was graded as serviceable or nonserviceable, similar to the method used by Combs et al [12]. Serviceable hearing was defined as Gardner-Robertson grade I or II and the ability to use a telephone with the treated ear. If any of the 2 criteria were not met, the hearing status was deemed nonserviceable. The maximum tumor dimensions were obtained from pretreatment magnetic resonance imaging. Posttreatment imaging follow-up was done every 6 months or annually.

Cranial nerve V and VII function was graded as intact or impaired and assessed clinically; for patients who had not been seen in clinic in the 6 months preceding the analysis, telephone surveys were conducted. Cranial nerve V function was graded impaired if any ipsilateral facial numbness, tingling, or problems with mastication was present, and cranial nerve VII was graded impaired if facial muscle asymmetry or ipsilateral facial muscle weakness was present. These criteria were used for both clinical and telephone assessment. Toxicities after radiotherapy were graded with Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The Kaplan-Meier product-limit method was used to calculate the probability of local control at 3 years. Local control was defined as no progressive disease by imaging (as measured by Response Evaluation Criteria in Solid Tumors [RECIST]), no new onset of symptoms, and no surgical intervention [1, 22].

Results

Tumor Control

The median clinical follow-up duration was 68 months for living patients (range, 36–106 months). The median radiographic follow-up was 26 months (range, 2–113 months). **Figure 1** shows the Kaplan-Meier curve for local control. Three-year actuarial local control was 85%.

One patient (No. 14) died of unrelated causes 5 months after completing PT. At the 3-month follow-up, he had no evidence of clinical or radiographic tumor progression. Among the remaining 13 patients, 2 patients (No. 8 and No. 9) underwent subsequent surgical resections. Both patients were referred for radiotherapy after they declined the recommended upfront surgical management. Patient No. 8 had been symptomatic for 4 years before undergoing definitive PT. She presented with ipsilateral facial numbness and gait instability at the time of consultation for PT. She had a right-sided cerebellopontine angle mass that measured 3.4 cm with a volume of 16 cm^3. Despite symptoms and compression of the pons, she refused surgery

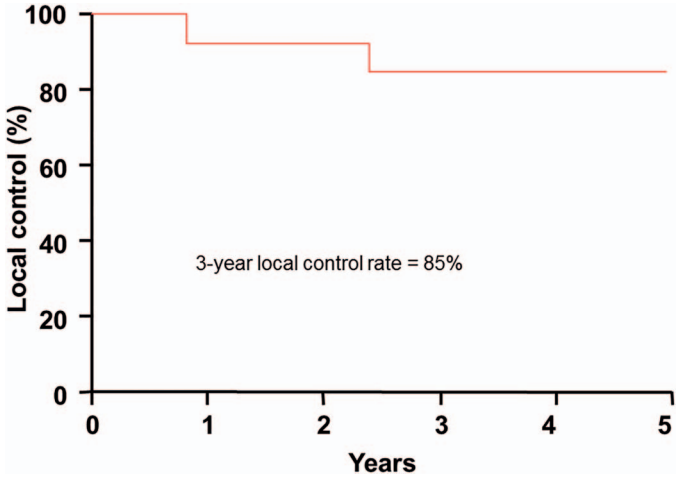

Figure 1. Kaplan-Meier curve for local control. The 2-year and 5-year actuarial local control rates were 92% and 85%, respectively.

and had PT instead (**Figure 2A**). At her 3-month follow-up, the tumor had decreased in volume from 16 cm^3 to 9.4 cm^3. Seven months later (10 months after PT), it had grown back to 12.6 cm^3 with a large necrotic-appearing component. The ventricular volume had also increased Imaging showed ventriculomegaly and the patient had incontinence and worsening gait instability. She underwent surgical salvage 10 months after completing PT. Patient No. 9 had a medial cystic tumor with a maximum pre-PT tumor volume of 4.9 cm^3. He presented with ipsilateral facial numbness. His tumor had regressed to 1.4 cm^3 at 2 years after treatment before increasing to 5.9 cm^3 4 months later (28 months after PT). The growth was predominately cystic as shown in **Figure 2B**. He had no clinical progression but elected to undergo surgical resection. Both patients are currently alive and without disease progression following surgery.

The maximum tumor dimension before and after PT for each patient is listed in **Table 1**. Three patients (21%) demonstrated partial response (by RECIST) on their most recent brain magnetic resonance imaging. All patients had stable disease or partial response at last follow-up, including the 2 patients who underwent post-radiation surgical resection (**Figure 1A** and **1B**).

Hearing Preservation

Table 2 details hearing status before and after PT. Among the 6 patients who initially presented with serviceable hearing, 2 (33%) retained serviceable hearing at the last follow-up, with a median follow-up of 70 months (range, 30–98 months) after PT.

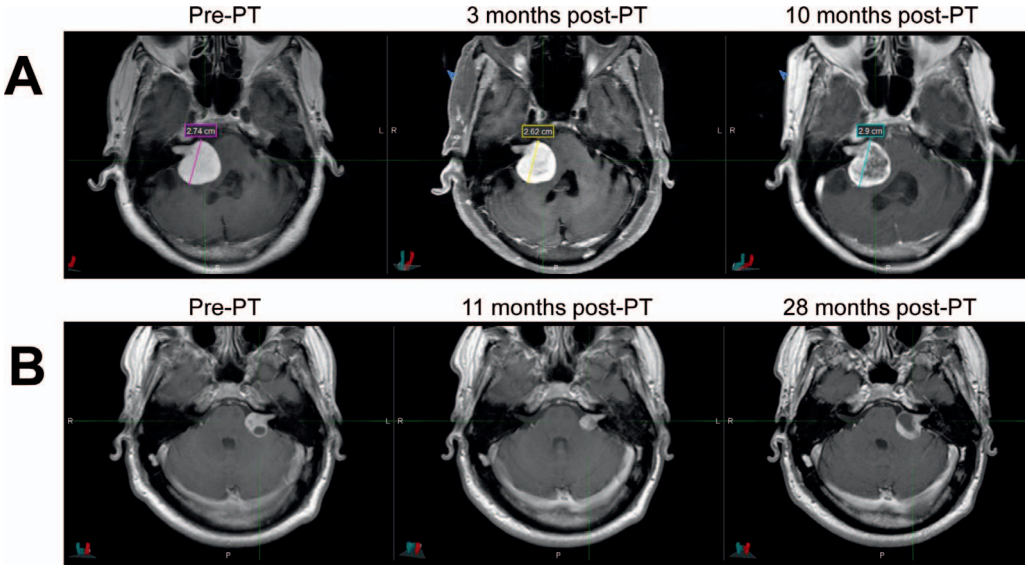

Figure 2. Patients with local failure after proton therapy. (A) Patient No. 8 experienced tumor regression at 3 months after proton therapy (from 16.0 cm^3 to 9.4 cm^3) before the tumor regrew (12.6 cm^3) and the patient developed worsening symptoms. The patient underwent salvage resection 10 months after proton therapy. (B) Patient No. 9 had a medial tumor with a cystic component that regressed before regrowing. The patient underwent surgical resection 28 months after proton therapy.

Table 2. Maximum tumor dimension and hearing status before and after proton therapy.

Patient No.	Pre-PT maximum tumor dimension (cm)	Post-PT maximum tumor dimension (cm) at last F/U	Pre-PT tumor volume (cm^3)	Post-PT tumor volume (cm^3) at last F/U	Local control by RECIST	Pre-PT hearing status (Gardner-Robertson grade)	Post-PT hearing status (Gardner-Robertson grade)
1	1.6	1.6	1.0	1.0	SD	S (II)	NS (III)
2	2.8	2.4	15.5	6.2	PR	NS	NS
3	2.5	2.5	2.1	4.0	SD	S (I)	S (II)
4	1.7	1.2	0.7	0.5	PR	NS (II)	NS
5	1.1	1.1	0.7	0.7	SD	NS (II)	NS
6	2.5	2.2	5.8	5.2	SD	S (II)	NS (III)
7	1.9	1.6	1.1	0.5	SD	NS (III)	NS
8	3.4	[a]3.4 at 10-month F/U	16.0	9.4 at 3-month F/U; [a]12.6 at 10month F/U	SD	NS	NS
9	2.4	[a]2.7 at 28-month F/U	4.9	1.35 at 11-month F/U; [a]5.9 at 28-month F/U	SD	S (I)	NS
10	1.9	1.9	1.0	1.4	SD	S (I)	NS
11	3.8	1.6	11.8	2.3	PR	NS	NS
12	1.6	1.5	0.9	0.9	SD	S (I)	S
13	0.8	0.6	0.1	0.1	SD	NS (III)	NS
14	3.0	3.0	6.9	6.9	SD	NS	NS

Abbreviations: PT, proton therapy; F/U, follow-up; RECIST, Response Evaluation Criteria In Solid Tumors; S, serviceable hearing; SD, stable disease; S, serviceable hearing; PR, partial response; NS, non-serviceable hearing.

[a]Immediately before salvage surgery.

Cranial Nerve Preservation

Two patients presented with cranial nerve V impairment and 1 with cranial nerve VII impairment prior to PT. No cranial nerve V or VII injury developed as a result of PT.

Toxicity

The only reported acute toxicities from PT included a grade 2 headache that was successfully treated with corticosteroids and 2 grade 1 skin changes (epilation and erythema) within the treatment field. No toxicity of grade 3 or above was reported.

Treatment Planning Comparison

Dose-volume histogram comparisons were made between proton plans (passively scattered) and photon plans (VMAT). Each of the treatment plans met target coverage goals (100% of the PTV covered by 95% of the prescription dose; $\geq$99% of the GTV covered by the prescription dose). The comparison dose-volume histogram data are shown in **Table 3**. No clinically appreciable differences were seen between PT and VMAT for brainstem maximum dose, mean cochlea dose, or cochlea max

Table 3. Dosimetry comparison of photons and protons.

Organs at risk	VMAT, Gy(RBE)	Proton therapy, Gy(RBE)
Brainstem max	51.9	51.4
Cochlea mean	49.5	49.6
Cochlea max	50.8	51.4
Brain V5	24.3	14.1
Brain V20	9.9	6.5
Brain V30	5.3	4.3
Integral dose	15.6	7.3

Abbreviation: VMAT, volumetric modulated arc therapy.

Table 4. Literature review of outcomes of proton radiation therapy for vestibular schwannoma.

Study	No. of patients (lesions)	Tumor volume (cm^3)	RT modality	Dose and fractions	Local control rate	Useful hearing preservation	CN V and VII preservation	Radiographic regression rate	Follow-up duration (months)
Current study	14 (14)	6.4 (mean), 3.9 (median)	Proton, fractionated	50.4 Gy (28 fractions)	92% at 2 years 85% at 5 years	33%	CN V, 100%; CN VII, 100%	50% after 26 months (median)	69 (mean), 68 (median)
Bush et al 2002 [8]	30 (31)	4.3 (mean)	Proton, fractionated	54.0 CGE (30 fractions) or 60.0 CGE (30–33 fractions)	100%	31%	CN V, 100%; CN VII, 100%	37%	34 (mean)
Vernimmen et al 2009 [9]	51 (not reported)	5.9 (mean)	Proton, FSRT	Mean, 26 CGE (3 fractions)	98% at 5 years	42% at 5 years	CN V, 93% at 5 years; CN VII, 90.5% at 5 years	–	72 (mean)
Weber et al 2003 [10]	88 (88)	1.4 (median)	Proton, SRS	Median, 12 CGE (1 fraction)	95.3% at 2 years 93.6% at 5 years	33% at 5 years	CN V, 91.1% at 5 years; CN VII, 89.4% at 5 years	71.3% at 2 years, 94.7% at 5 years	38.7 (median)
Harsh et al 2002 [11]	68 (not reported)	2.49 (mean)	Proton, SRS	12 CGE (1 fraction)	94% at 2 years 84% at 5 years	33%	CN V, 89.7%; CN VII, 89.7%	54.7% at 34 months (mean)	44 (mean)

Abbreviations: RT, radiotherapy; CN, cranial nerve; CGE, cobalt Gray equivalent; FSRT, fractionated stereotactic radiotherapy; SRS, stereotactic radiosurgery.

dose. In 13 of 14 patients, the cochlea was within the PTV volume and minimal cochlear sparing was achieved. Average brain V5 and V20, but not V30, was lower in the PT plans. Average integral dose (defined as Body-CTV) was also lower in the PT plans.

Discussion

We report our institution's clinical outcomes for patients treated with definitive standard-fractionation PT for VS. The current series adds to the only other published series of standard-fractionation PT for VS and contributes considerably longer follow-up [8]. To date, there are 3 published reports on outcomes after hypofractionated radiotherapy or stereotactic radiosurgery with protons for treatment of VS. **Table 4** compares our results to those studies. Our series confirms that fractionated proton radiotherapy is very well tolerated, with no grade 3 or higher complications and 100% cranial nerve V and VII preservation. The 3-year local control rate of 85% is on the lower end of the expected range, while the serviceable hearing preservation rate of 33% is lower than expected compared with many large published photon series (**Table 4**). These findings merit further consideration.

The reported tumor control rate for VS treated with definitive fractionated radiotherapy in a large series ranges from 84% to 95% [14, 15, 23, 24]. The local control in our series is certainly within an acceptable range, though it is perhaps slightly lower than expected, likely as a result of patient and tumor characteristics. In their series, Bush et al [8] achieved a 100% local control rate with a mean follow-up time of almost 3 years. Notably, they treated to doses of 54–60 Gy(RBE), higher than our standard dose of 50.4 Gy(RBE). While it is impossible to exclude the reduced dose in our series as a contributing factor to local failures, it is also an unlikely contributor given the volume of data supporting the use of 50 Gy with photons [14, 24, 25]. More likely, our modest local control rate is attributable to a combination of relatively large tumors and small patient numbers. Our series includes tumors with a mean maximum size of 2.2 cm and a mean volume of 4.9 cm^3, larger than most published series. Several series have demonstrated that increased tumor size and/or volume is associated with increased local failures. The series from investigators at Massachusetts General Hospital (Boston) showed that tumor volume has a significant impact on local control after fractionated radiotherapy, with a cut-off point of $\geq$8 cm^3 and $<$8 cm^3 correlating to 5-year local control rates

Table 5. Patients with serviceable hearing before proton therapy, cochlear dose, and hearing outcomes.

Patient No.	Mean cochlear dose (CGE)	Maximum cochlear dose (CGE)	Pre-PT hearing status	Post-PT hearing status	Length of F/U (months)
1	50.9	51.5	S	NS	43
3	52.0	53.0	S	S	68
6	27.8	36.2	S	NS	36
9	51.6	52.3	S	NS	71
10	51.0	52.6	S	NS	96
12	51.1	51.9	S	S	98

Abbreviations: CGE, cobalt Gray equivalent; PT, proton therapy; F/U, follow-up; S, serviceable hearing; NS, non-serviceable hearing.

of 97% and 47%, respectively [26]. Radiosurgery series have similarly shown larger tumor sizes and volumes to be predictive of local failures [27, 28].

The 2 cases of local failures in our cohort occurred in a patient with a large tumor and another whose tumor had a significant cystic component. Patient No. 8 saw her tumor regress after PT only to see it increase in volume, at which time she became increasingly symptomatic. Patient No. 9 experienced tumor regression followed by significant progression within the cystic component that led to surgical salvage, despite no worsening symptoms. As has been previously reported, transient regression or progression can occur (especially in cystic tumors) and may not represent treatment failure. This phenomenon can contribute to an artificially inflated failure rate. Shirato et al [29] found that the 3-year rate of transient tumor growth after fractionated radiotherapy is 45% and 25% for cystic and solid tumors, respectively. However, with long-term follow-up, overall local tumor control exceeds 90% at 3 years. Furthermore, several reports showed that cystic lesions sometimes undergo rapid transient growth after radiation but may regress without any intervention [30–32].

Although the hearing preservation rate of 33% in our cohort is consistent with that of the Loma Linda series [8], it is lower than expected for conventionally fractionated radiotherapy (large series report rates from 68% to 95%). In the Loma Linda series, 31% of patients with Gardner-Robinson grade 1 or 2 hearing at the time of treatment had preserved grade 1 or 2 hearing. While the combined number of patients with serviceable hearing prior to RT from our 2 series is too small to draw conclusions, the data suggest the possibility of worse serviceable hearing preservation using PT. The relatively low hearing preservation rate in our series, though, seems unlikely related to treatment modality (protons versus photons) and more likely attributable to several other factors. First, and perhaps most significantly, was the inadequate sparing of the cochlea. There is strong evidence indicating that hearing loss after fractionated radiotherapy for VS correlates with cochlear dose [14, 33, 34]. In our series, the average mean ipsilateral cochlear dose was 49.7 Gy (range, 27.8–52.2 Gy) and the average maximum ipsilateral cochlear dose was 51.3 Gy (range, 36.2–53.7 Gy) (**Table 5**). Bennion et al [33] reported improved hearing preservation with mean cochlear doses below 40 Gy. The large target volumes in our series and relatively large PTV expansion of 5 mm contributed to the high mean cochlear doses. Since treating the last patient in this series, our institutional target volume has changed to include a GTV to PTV expansion of 3 mm. Additionally, more attention is now given to avoiding the cochlea during treatment planning.

Our criterion for assessing hearing preservation was particularly stringent, utilizing both patient-reported hearing function and audiometry-based measures. All of the patients included in our series underwent audiometry testing within 6 months of their last follow-up. The definition of useful hearing in the literature varies widely across series and often includes either only patient-reported subjective measures or audiometry-based measures, as well as unclear criterion. Several smaller series using rigorous audiometry testing and long-term follow-up have reported hearing preservation rates comparable to ours. Rasmussen et al [34] reported a 5-year hearing preservation rate of ~20%. Bennion et al [33] reported a 3-year hearing preservation rate of 51% with a median time to loss of serviceable hearing of 42.2 months following fractionated radiotherapy. Differences in assessing hearing preservation complicate direct comparison between studies. The long follow-up in our series and small patient numbers also likely contribute to our relatively low hearing preservation rates.

Our data contribute to the growing body of literature detailing outcomes with the use of PT for VS. They will enable refined selection criteria for patients most appropriate for PT. There is a robust body of literature indicating the effectiveness of photon radiotherapy with either standard fractionation or stereotactic radiosurgery for VS. Although PT is not expected to improve local control outcomes, it may improve hearing preservation by enabling improved avoidance of the cochlea using more deliberate planning as well as advances in delivery techniques (eg, intensity-modulated PT) compared with photon-based

radiation. The reduced integral dose of PT may also benefit younger patients who are at a higher risk for radiation-induced malignancies. Although beyond the scope of the current study, future studies should compare contemporary proton radiation planning with photon-based stereotactic radiosurgery to evaluate differences in dose distribution to the target and organs at risks.

Perhaps most importantly, our results highlight the need for appropriate patient selection when considering the various modalities for the definitive management of VS. Patients with large, bulky tumors causing mass effect (or impending mass effect) should be thoroughly counseled on the role of surgery in the management of their disease. Patients with cystic lesions are at risk for cyst progression even when the solid tumor components are controlled [29, 35]. Patients and physicians must be aware of possible cyclical changes (growth and regression) following radiotherapy and the need for close clinical and imaging follow-up. Surgical intervention in these scenarios must be individualized. Based on our data, PT may not be preferred over photon-based radiotherapy for all patients with VS. Treatment decisions and comparison planning should be done on a case-by-case basis. The use of protons for the explicit benefit of decreasing low and moderate brain doses and lowering the integral dose should be individualized.

Conclusion

Our results show that standard-fractionated stereotactic PT for VS is well tolerated and offers good local control. Further investigation is necessary to determine what benefits protons may provide over photons. Comparative data with photon radiation and optimal patient selection is critical to improving outcomes.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of interest: Dr William Mendenhall is operating editor of the *International Journal of Particle Therapy*. The authors have no other conflicts of interest to disclose.

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