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CLINICAL STUDY

Increased cochlear radiation dose predicts delayed hearing loss following both stereotactic radiosurgery and fractionated stereotactic radiotherapy for vestibular schwannoma

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Abstract

Purpose Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (fSRT) are noninvasive therapies for vestibular schwannomas providing excellent tumor control. However, delayed hearing loss after radiation therapy remains an issue. One potential target to for improving hearing rates is limiting radiation exposure to the cochlea.

Methods We retrospectively reviewed 100 patients undergoing either SRS with 12 Gy (n = 43) or fSRT with 50 Gy over 28 fractions (n = 57) for vestibular schwannoma. Univariate and multivariate analysis were carried out to identify predictors of hearing loss as measured by the Gardner Robertson scale after radiation therapy.

Results Deterioration of hearing occurred in 30% of patients with SRS and 26% with fSRT. The overall long term (> 2 year) progression rates were 20% for SRS and 16% for fSRT. Patients with a decrease in their Gardner Robertson hearing score and those that loss serviceable hearing had significantly higher average minimal doses to the cochlea in both SRS and fSRT cohorts. ROC analysis showed that a cut off of 5 Gy and 35 Gy, for SRS and fSRT respectively, predicted hearing loss with high sensitivity/specificity.

Conclusion Our data suggests the minimal dose of radiation that the cochlear volume is exposed to is a predictor of delayed hearing loss after either SRS or fSRT. A threshold of 5 Gy/35 Gy may lead to improved hearing preservation after radiotherapy. Further prospective multi center studies can further elucidate this mechanism.

Keywords Vestibular schwannoma · Stereotactic radiosurgery · Fractionated radiotherapy · Serviceable hearing · Cochlea

Introduction

Vestibular schwannomas are benign intracranial neoplasms that derive from schwann cells of the vestibular nerve. Given this anatomical relationship, the most common symptom of vestibular schwannomas is hearing loss, but progression of tumor growth can lead to facial nerve dysfunction, cerebellar dysfunction, brainstem compression, and hydrocephalus [1]. Management options for vestibular schwannomas include: observation with serial imaging, surgical resection, and radiotherapy.

Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (fSRT) are nonintrusive treatment options for vestibular schwannoma. These options have shown to successfully prevent tumor growth in > 90% of patients while avoiding complications associated with microsurgery [2–5]. In a systematic review on 19 cases series on SRS and fSRT, both therapies provided a 95% chance of preventing further therapy due to tumor progression. The risk of facial nerve dysfunction on average was 3.6% for SRS and 11.2% for fSRT and risk of trigeminal nerve dysfunction was 6.0% for SRS and 8.4% for fSRT [3].

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Despite low complication rates with good tumor control, hearing deterioration remains a major side effect of SRS and fSRT. This usually does not occur immediately after treatment, but rather in a delayed manner. The etiology of this delayed hearing loss is unclear, but may be related to vascular insufficiency, injury to cochlear hair cells, or damage to the vestibulocochlear region itself [6, 7].

Hearing loss after radiotherapy for vestibular schwannoma may be related to dose, volume, and location. One study identified hearing loss to be correlated with intracanalicular tumor volume and dose delivered to this volume [8]. Radiation doses to the cochlea may be correlated with the unfavorable effects of SRS and fSRT due to the fragile nature of various cochlear structures such as the hair cells of the organ of Corti and the stria vascularis [9]. Paek et al. studied the relationship between radiotherapy and these various structures including the cochlea, vestibulocochlear nerve, and the cochlear nucleus in the brainstem [7]. This study found that only the maximum radiotherapy dose delivered to the cochlear nucleus was a predictive factor in regard to hearing deterioration. Similarly, Massager et al. found that increased radiation dose delivered to the cochlea was associated with worsening of hearing [10]. The cochlear dose was also associated with hearing loss in fSRT [11, 12].

Despite the significant data associating radiation to the cochlea with hearing loss, it is unclear the dosimetric and volumetric relationships that exist at this location. Several studies have suggested limiting SRS mean dose to the cochlea to less than 3–5 Gy [13–17]. One study suggested worsening hearing loss with interval increase in cochlear volume irradiated [16]. Fewer studies exist in regards to fSRT, but do suggest a mean cochlear dose < 45 Gy over 25–30 fractions to minimize hearing loss [11, 12, 18]. Our group studied a small sample of patients with either SRS or fSRT and found that the minimum, in addition to mean dose was predictive of hearing loss in SRS [19]. In this study we present a large cohort of patients with serviceable hearing undergoing SRS or fSRT for vestibular schwannoma. We compare the two modalities and evaluate dosimetric relationships in regards to radiotherapy to the cochlea in hopes to elucidate the optimal radiation therapy protocol for vestibular schwannoma.

Methods

Patient selection

Institutional review board approval was acquired for this retrospective study. We identified all patients with vestibular schwannomas who underwent SRS or fSRT between 2007 and 2019 at the University of California Los Angeles. All patients had therapy by one of the senior authors (T.K.; P.L.; N.P.; M.S..; and/or I.Y.). Inclusion criteria included: (1) patients with vestibular schwannoma as the most likely diagnosis based on imaging or in case of previous surgery, pathological diagnosis; (2) either therapeutic SRS or fSRT for vestibular schwannoma; (3) clear pre-treatment and post-treatment assessment of hearing status (4) radiologic assessment of tumor progression (5) documented radiotherapy plans for assessment of cochlear dosing (Fig. 1). Of the 114 patients with radiotherapy for vestibular schwannoma, 100 patients met the inclusion criteria and were included in this study. Clinic visits, audiograms, imaging, and radiotherapy plans were reviewed for patient data.

Treatment parameters

All patients underwent either SRS or fSRT by senior authors (T.K.; P.L.; N.P.; M.S.; and/or I.Y.) at University of California Los Angeles. Frame based SRS was used prior to 2008 and frameless beyond as well as for all fSRT. Imaged guided radiotherapy was used for all frameless cases. Planning imaging included 1.5 mm slice thickness computed tomography (CT) and either 1.5 or 3.0 T magnetic resonance (MR) imaging scans. The CT and MR imaging scans were fused to allow adequate resolution of tumor and normal anatomy including bony features. Radiotherapy was carried out with a 6-MV Novalis (2007—2009) or a 6-MV Novalis Tx

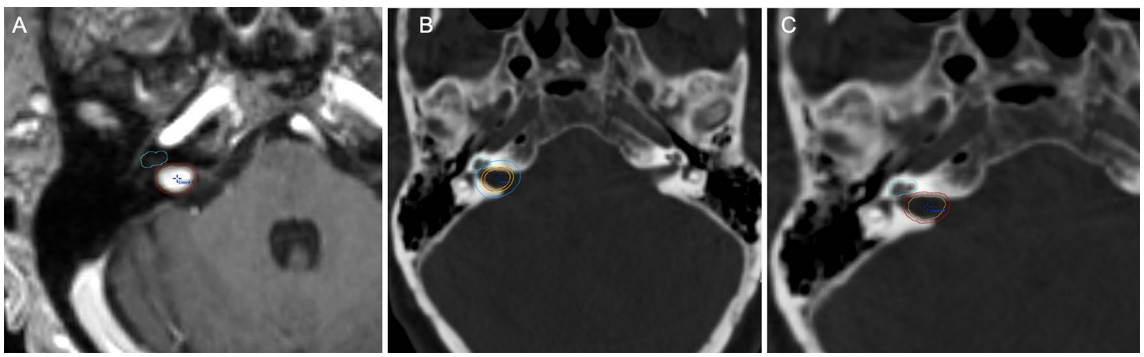

Fig. 1 Example planning of radiation treatments

(2009—Present) linear accelerator (Brainlab, Munich, Germany) using a micro multileaf collimator (3 mm leaf width) or HD120 multileaf collimator (2.55 mm leaf width) respectively. Plans were generated using BrainSCAN 5.31 treatment planning software from 2007–2009 and using iPlan RT Dose software from 2009—Present (Brainlab, Munich, Germany). SRS plans included a 1 mm planning margin and fSRT plans included a 2 mm margin. Plans were approved by both radiation oncologist (T.K.; P.L.; M.S.) approved and a neurosurgeon (A.D.; N.P.; I.Y.). Patients undergoing SRS received a marginal dose of 12 Gy to the 90% isodose line. Patients undergoing fSRT received a marginal dose of 50.4 Gy to the 90% isodose line (1.8 Gy over a course of 28 fractions).

Hearing & radiologic outcomes

Per the inclusion criteria of this study, each patient included had both pre-operative and post-operative hearing status documented by physical exam and/or pure tone audiogram (PTA and speech discrimination score (SDS) results. The Gardner Robertson (GR) scale was used to quantitate hearing status. GR I was assigned to patients with no hearing issues and/or PTA 0–30/SDS 70–100%. GR II was assigned to patients with hearing loss but serviceable hearing (able to use phone) and/or PTA 31–50/SDS 50–69%. GR III was assigned to patients with subjective hearing although not serviceable (can hear finger rub but cannot use phone) and/or PTA 51–90 and SDS 5–49%. GR IV was assigned to patients with profound hearing loss although not complete deafness (can hear finger snap) and/or PTA 90–100/SDS 1–4%. GR V was assigned to patients with complete deafness. If PTA and SDS did not fall within the same GR score, the higher GR score was chosen. Maximum tumor diameter was calculated at the described time points, including pre-treatment and every post-treatment scan available. An change in tumor size was identified as a change in the maximum diameter from the previous time point. Median follow up for hearing outcomes in patients undergoing audiologic analyses was 25 months (range 7–106 months). Of these patients, 66% had $\geq$ 1 year follow up and 100% had $\geq$ 6 month follow up. Hearing outcomes within the first year and at last available follow up were reported. Radiologic follow up for patients included in radiologic analyses ranged from 7–118 months (mean 30 months). Of these patients, 75% had $\geq$ 1 year follow up and 100% had $\geq$ 6 month follow up.

Dosimetry calculations

The cochlea was initially identified and contoured using bone window CT imaging scans at 1.5 mm thick slices. When available, additional confirmation of correct contouring was referenced using T2 weighted MR imaging. The volume of the cochlea was segmented and recorded as described previously [20]. The treatment planning software, BrainSCAN or iPlan RT Dose (Brainlab, Munich, Germany) was used to calculate the minimum, mean, and maximum doses received by the previously set cochlear volume. Independent sample *t* tests were used for to compare SRS and fSRT groups and paired sample *t* tests were used to compare differences within patients over time. No correction for multiple comparisons was applied. A P-value of < 0.05 was used to note statistical significance. All statistical analysis was carried out on SPSS Statistics for Macintosh (Version 26.0. Armonk, NY: IBM Corp).

Results

Patient characteristics

We reviewed all patients undergoing SRS or fSRT for vestibular schwannoma from 2007 to 2019. Following application of the inclusion criteria (see "Methods"), 100 patients were included in this study and overall patient characteristics are described in Table 1. The average age at start of radiation therapy was 58 years (range 13–86 years). Half the patients were female and half were male. Patients recalled subtle symptoms that began on average 2 years before treatment. Presenting symptoms included: hearing loss (86%), tinnitus (38%), vertigo (18%), facial numbness or paresthesias (14%), ataxia (13%), facial weakness (7%). Tumor characteristics included: 58% of tumors treated were left sided, 42% were right sided and 5% of tumors were cystic prior to radiation therapy. The average maximal diameter of the tumor was 18 mm (range 3–47 mm). Fifteen patients (15%) had previous resection and no patient had prior radiation therapy. The average time between resection and radiotherapy was 28 months (range 3–97 months). SRS was delivered to 43% of patients and fSRT to 57% of patients. No patient required surgery or repeat radiation therapy for recurrent or residual tumor.

SRS and fSRT result in comparable side effect profiles and tumor control rates

There were 43 patients who had SRS (12 Gy in 1 fraction) and 57 patients who had fSRT (50.4 Gy in 28–30 fractions) for vestibular schwannoma. The patient and tumor characteristics of the two cohorts were compared (Table 1). The only significant differences in patient characteristics included: (1) patients with SRS were older than patients with fSRT (mean 62 years versus 54 years; $p = 0.01$) and (2) patients with SRS presented with more tinnitus than patients with fSRT (51% versus 28%; $p = 0.02$). While there was no significant difference in previous surgery

Table 1 Patient characteristics

Characteristic	Overall (n = 100)	SRS (n = 43)	fSRT (n = 57)	p-value
Age	58	62	54	**0.01**
Female	50%	44%	54%	0.31
Time to treatment (months)	24	25	22	0.58
Pre-operative symptoms				
Hearing loss	86%	91%	82%	0.24
Tinnitus	38%	51%	28%	**0.02**
Vertigo	18%	23%	14%	0.35
Facial numbness	14%	21%	9%	**0.08**
Ataxia	13%	9%	16%	0.35
Facial weakness	7%	12%	4%	0.11
R sided tumor	42%	40%	44%	0.67
Cystic tumor	5%	5%	5%	0.89
Maximal diameter (mm)	18	17	19	0.28
Prior resection	15%	21%	11%	0.15

Bold represents the p-value of < .05

between patients who would undergo SRS or fSRT, patients with previous surgery had a higher pre treatment Gardner Robertson score (3.7) and lower level of pre treatment serviceable hearing (33%). In patients who would receive SRS, 91% of patients had pre-operative hearing loss while 82% of patients who would receive fSRT had pre-operative hearing loss ($p = 0.24$). The average Gardner Robertson hearing score for patients who would receive SRS was 3.6 and the average score for patients who would receive fSRT was 2.6 ($p < 0.01$). The percentage of patients who had serviceable hearing was 40% in patients who would receive SRS and 74% in patients who would receive fSRT ($p < 0.01$).

Given differences in baseline hearing levels in patients undergoing SRS or fSRT we evaluated change in hearing status taking into account these baseline differences. In patients who were not completely deaf (Gardner Robertson hearing score < 5), hearing deterioration, as defined as an increase in the Gardner Robertson hearing score by 1 or more, occurred in 22% of patients after SRS and 20% of patients after fSRT ($p = 0.82$) by 1 year. This increased to 30% of patients after SRS and 26% of patients after fSRT ($p = 0.74$) at last follow up (mean 26 months). In patients who had serviceable hearing (Gardner Robertson hearing score < 3), hearing deterioration, and therefore loss of serviceable hearing, occurred in 35% of patients after SRS and 24% of patients after fSRT ($p = 0.38$). This increased to 47% of patients after SRS and 29% of patients after fSRT ($p = 0.18$). There were no significant differences in hearing outcomes between SRS and fSRT (Fig. 2a–d). There were no differences between SRS and fSRT in post-therapy rates of total (including new and worsening) non-hearing symptoms including: tinnitus, headache, ataxia, vertigo, facial numbness or paresthesias, facial weakness, or hydrocephalus (Table 2).

Serial surveillance MR imaging scans were analyzed to record changes in tumor size after treatment. The average pre-treatment tumor max diameter in SRS patients was 17.0 (6–39 cc) and 19.1 (3–47 cc) in fSRT patients ($p = 0.28$). The average imaging follow up was 24 months. In patients with SRS, 31% of tumors decreased in size, 44% of tumors remained stable, and 21% of tumors increased in size. In patients with fSRT, 25% of tumors decreased in size, 63% of tumors remained stable, and 16% of tumors increased in size. The long term progression rate was 21% in SRS and 16% in fSRT ($p = 0.34$) (Fig. 2e). Each tumor was evaluated for increase in size, decrease in size, or stability in size at up to 5 different time points (6 months, 12 months, 18 months, 24 months, and 36 months). There was increased tumor size in 22.2% of patients at 6 months, 15.3% of patients at 12 months, 18.4% of patients at 18 months, 13.2% of patients at 24 months, and 8.7% of patients at 36 months. There was decreased tumor size in 5.6% of patients at 6 months, 15.3% of patients at 12 months, 23.7% of patients at 18 months, 34.2% of patients at 24 months, and 39.1% patients at 36 months. We categorized tumors as increasing, decreasing, or stable over the five time points and report the average score (Fig. 2f). With these data together, we found that tumors tend to initially increase slightly then decrease steadily over time.

Predictors of hearing loss

Using independent sample t-test and chi-squared test we found that no form of pre-therapy patient or tumor characteristic was predictive of hearing loss as defined by either

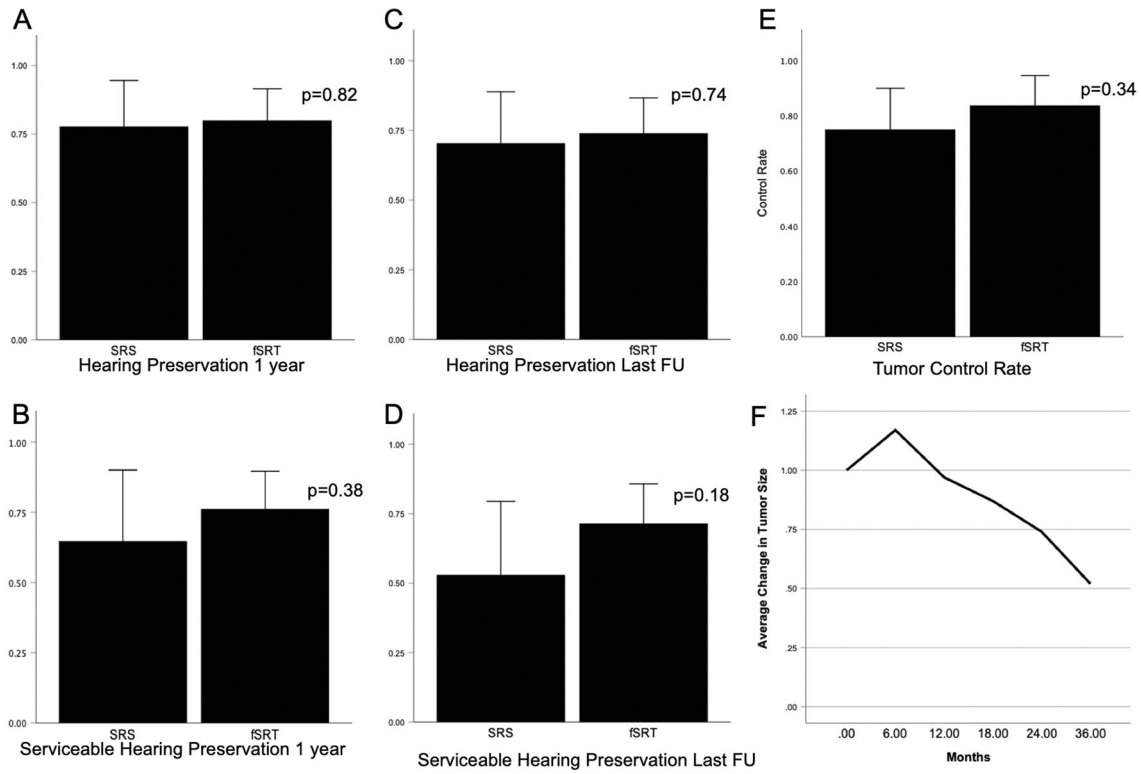

Fig. 2 Hearing preservation comparisons between SRS and fSRT at **a** within 1 year overall preservations, **b** serviceable hearing within 1 year, **c** hearing preservation overall at last available follow up, **d** serviceable hearing preservation at last available follow up, **e** tumor control rate, and **f** overall tumor size after treatment

Table 2 Post operative symptoms after treatment

Symptom	SRS (n = 43) (%)	fSRT (n = 57) (%)	p-value
Tinnitus	29	27	0.88
Headache	14	8	0.40
Ataxia	9	8	0.97
Vertigo	14	17	0.77
Facial numbness	20	23	0.75
Facial weakness	14	8	0.40
Hydrocephalus	2	2	0.84

loss of Gardner Robertson score or loss of serviceable hearing in either the 1 year or long term (mean 2 year) follow up (Table 3). We mention that both age and pre-operative tinnitus did not change hearing outcomes, although these were different in our populations undergoing SRS and fSRT. We next evaluated the effect of cochlear dose on hearing outcomes.

In patients who received SRS, the average volume of identified cochlea was 0.09 cc (SD 0.06). The average minimal dose to the cochlea was 5.0 Gy, the average mean dose to the cochlea was 8.2 Gy and the average max dose to the cochlea was 11.6 Gy. The average minimal, mean, and maximal dose to the cochlea was significantly higher in patients who had decreased GR score after SRS at 1 year ($p < 0.01$ each) and last follow up ($p < 0.01$; $p = 0.05$; $p = 0.01$). Each of these variables were also higher in patients who had loss of serviceable hearing after SRS at 1 year ($p < 0.01$; $p = 0.01$; $p = 0.05$) and last follow up ($p = 0.04$; $p = 0.04$; $p = 0.08$) (Fig. 3a–d). Of these three predictive variables, minimal dose received by the cochlea was the most robust. We analyzed how well this variable could predict hearing loss using ROC analysis (Fig. 3e). The area under the curve for was 0.982 ($p < 0.01$), signifying an excellent test for predicting hearing loss. With a cut-off of 5 Gy, there was a 100% sensitivity and 90% specificity in predicting hearing loss. If this cut-off was met, there was hearing preservation in 94% and if the cut-off was not met, there was hearing preservation in 13% at last follow up.

In patients who received fSRT, the average volume of the cochlea was 0.08 cc. The average minimal dose to cochlea was 14.8 Gy, the average mean dose to the cochlea was 23.2 Gy and the average max dose to the cochlea was 28.1 Gy. Only the average minimal dose to the cochlea was significantly elevated in patients who had increased GR score after fSRT at 1 year ($p = 0.03$) and at last follow

Table 3 Clinical predictors of hearing loss after treatment

	1 year		Last follow up	
	Decreased GR score p-value	loss of SH p-value	Decreased GR score p-value	loss of SH p-value
Age	0.93	0.56	0.76	0.79
Female	0.54	0.62	0.41	0.32
Time from initial symptoms to treatment	**0.08**	0.17	0.14	0.22
Pre-op symptoms				
Tinnitus	0.38	0.38	0.19	0.11
Vertigo	0.25	0.45	0.23	0.38
Facial numbness	**0.06**	0.21	0.22	0.48
Ataxia	0.71	0.73	0.61	0.97
Facial weakness	0.14	0.29	0.30	0.49
R sided tumor	0.72	0.65	0.89	0.80
Cystic tumor	0.97	0.71	0.71	0.50
Maximal diameter	0.27	0.15	0.62	0.46
Prior resection	0.80	0.71	0.55	0.50

Bold represents the p-value of < .05

Data represented by p-value from independent sample t test of clinical variables stratified by either decreased Gardner-Robertson (GR) score or loss of serviceable hearing (SH)

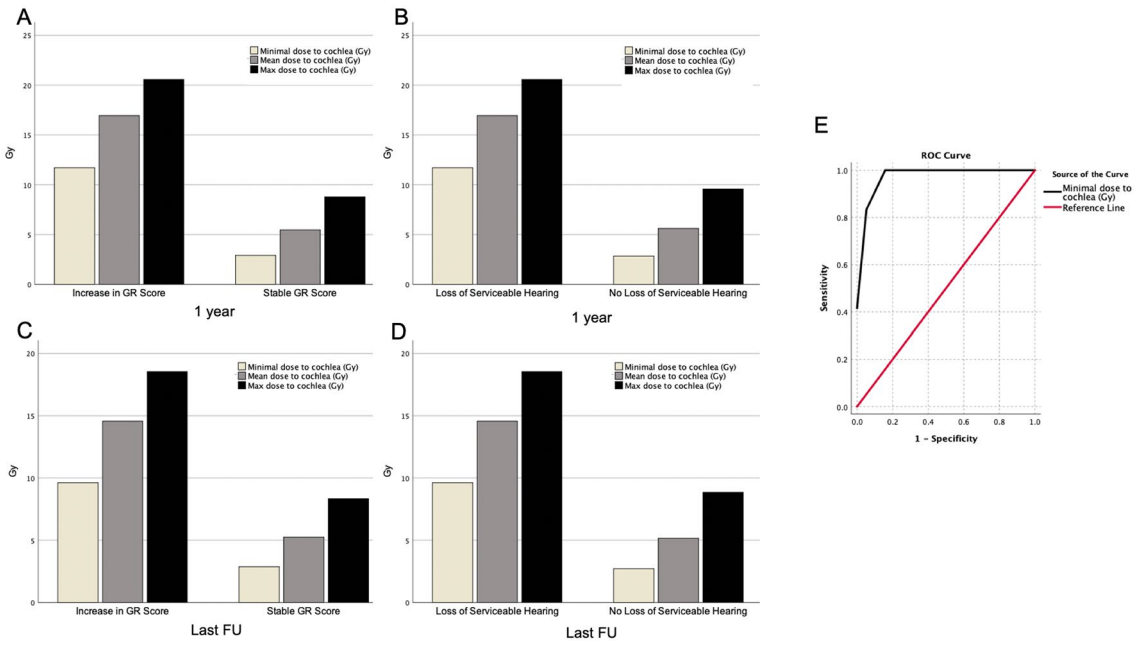

Fig. 3 SRS associated minimal, mean, and maximum radiation doses to cochlea were associated with higher increased GR score and loss of serviceable hearing at both **a**, **b** within 1 year and **c**, **d** last available follow up. **e** Minimal cochlear dose may be a useful predictor of hearing loss with a ROC curve for SRS patients

up (p = 0.01). Minimal dose to the cochlea was also significantly elevated in patients who lost serviceable hearing at 1 year (p = 0.01) and at last follow up (p = 0.04) (Fig. 4a–d). Maximum dose to the cochlea was not significantly different in patients with increased GR score or loss of serviceable hearing at either time point. Mean dose to the cochlea was only significantly elevated in patients who had lost serviceable hearing at last follow up (p = 0.03). A ROC analysis for

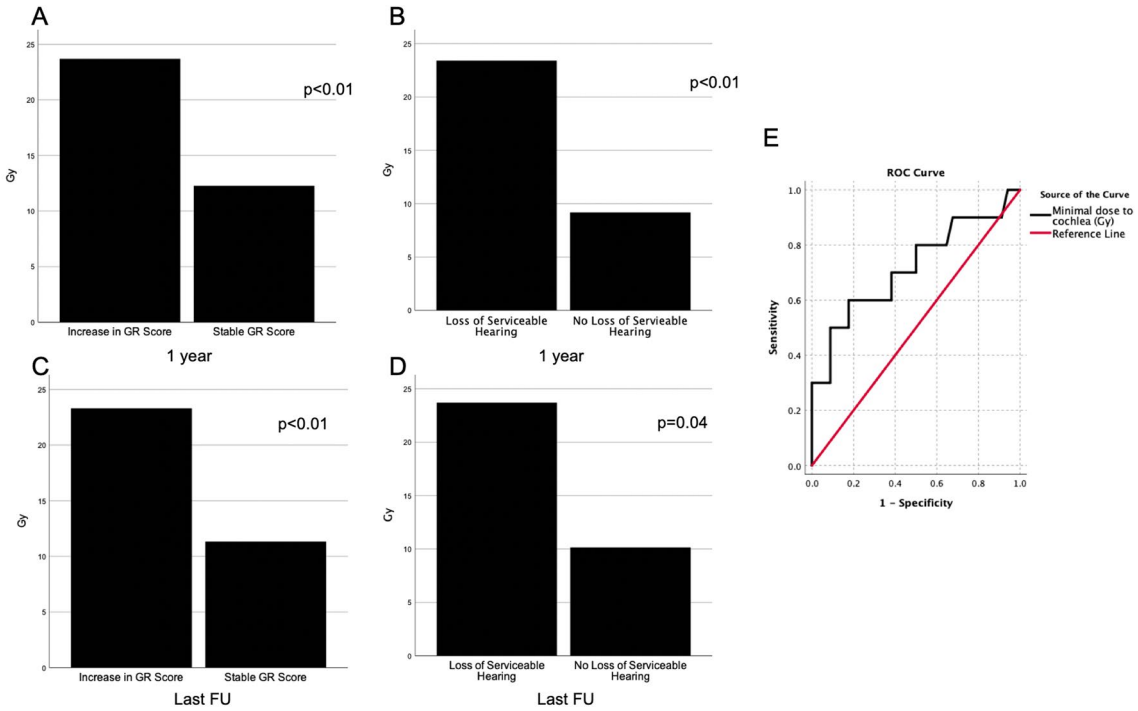

Fig. 4 There was significant increase of GR score and loss of serviceable hearing in the fSRT cohort at the **a**, **b** within 1 year and **c**, **d** last available follow up. **e** Minimal cochlear dose may be a useful predictor of hearing loss with a ROC curve for fSRT patients

minimal dose received by the cochlea had an area under the curve of 0.718 (p = 0.04) (Fig. 4e). A cut off of 35 Gy had a 91% specificity and 50% sensitivity for predicting hearing deterioration after fSRT. If this cut-off was met, there was hearing preservation in 77% and if the cut-off was not met, there was hearing preservation in 20% at last follow up.

Discussion

We report a series of 100 consecutive patients with either SRS or fSRT for vestibular schwannoma. In our cohort of 43 patients with SRS and 57 patients with fSRT, we describe outcomes similar to those previously published in the literature [2–5]. All patients undergoing SRS or fSRT did not need further therapy for tumor during our follow up period (mean 2 years). Serviceable hearing was lost in 30–40% of patients, similar to previous studies [3].

SRS and fSRT have both been considered comparable options for radiotherapy for vestibular schwannoma. A systematic review in 2017 identified 19 case series with long term outcome description involving SRS and fSRT and found no significant difference in outcomes in regards to hearing preservation and tumor control [3]. Our results are in concordance with the previous literature, identifying no significant difference in hearing outcomes, tumor control rates, and non-hearing symptoms between SRS and fSRT.

Given the delayed effects of radiotherapy, we evaluated changes in both hearing and tumor size over time. Similar to previous studies, we identified progressive and delayed decreases in hearing after radiotherapy [6, 7, 21]. This trend was present in both SRS and fSRT and occurred in patients who had mild deteriorations in hearing (GR I to II) as well as those who lost serviceable hearing. A study previously showed that increased time to treatment in patients with good hearing lead to decreased hearing preservation rates [22]. In this study we did find that in patients with serviceable hearing, those who had longer time from symptoms to treatment were more likely to have decreases in hearing, but this was trend was not statistically significant. Studies have previously reported different categories of changes in tumor size [23, 24]. One common finding is initial increase in tumor size which is thought to be due to swelling. In this study we describe a common description of initial modest increases in size of tumor followed by long term progressive involution. We see that this increase in size can be associated with transient worsening symptoms such as facial weakness, numbness, or pain that improves. We do not see this same pattern with hearing loss. Our hypothesis is that swelling after radiotherapy leads to transient symptomatology secondary to inflammation and mass effect, but this is not the reason for hearing loss after surgery as the time courses do not line up. Specifically, both hearing loss and tumor shrinkage are

delayed and then progressive. Hearing loss must be caused by factors unrelated to tumor swelling.

Several studies have associated radiation to the cochlea as a causative agent for hearing loss after SRS [13–16] or fSRT [11, 12, 18] for vestibular schwannoma. These studies have analyzed the mean dose delivered to the cochlea have suggested as to limiting doses for both therapy types. These studies have associated hearing loss with mean cochlear dose ≥ 3–5 Gy [17]. We have previously studied in a small sample of patients with either SRS or fSRT and found that the minimum dose delivered to the cochlea was a unique parameter that was predictive of hearing loss in SRS [19]. In our current study, we use a significantly larger cohort of patients to show robust relationships between the minimum dose received by the cochlea and hearing loss in both SRS and fSRT. This held true for both small changes in hearing (GR I to II) as well as loss of serviceable hearing. We used our large sample size to derive a threshold that was sensitive and specific for predicting hearing loss in SRS and in fSRT. We propose a limit of 5 Gy to the cochlea for SRS and 35 Gy in fSRT to maximize patients hearing preservation rates without preventing treatment level doses to tumor. These results are comparable to previously established guidelines for radiotherapy. The UK Consensus on radiotherapy constraints to normal tissue for the cochlea suggest a limit between 4–9 Gy for the mean single fraction radiation dose [25]. The European Particle Therapy Network consensus suggests the total average dose to the cochlea be limited to 45 Gy [26]. Similarly, a threshold of 32 Gy to the cochlea was proposed to avoid grade 2 tinnitus after radiotherapy [27]. Our thresholds derived from risk of hearing loss are comparable to the previously suggested guidelines. However, given our use of the minimum, rather than the mean dose to the cochlea, our thresholds, as expected, tend to be slightly lower. These data suggest that the findings in this paper are congruent with previous studies and clinical experience used to generate consensus statements on radiation to the cochlea and may allow for even more precision in treatment.

Conclusions

Both SRS and fSRT are comparable options for tumor control in patients in vestibular schwannomas. While this series shows both SRS and fSRT can provide good tumor control with minimal major complications, serviceable hearing rates were still 30–40%. Our data suggests the minimal dose of radiation is the most robust predictor of delayed hearing loss after either SRS or fSRT. By limiting the radiation dose to the cochlea in patients with serviceable hearing undergoing radiotherapy to 5 Gy for SRS and 35 Gy for fSRT, hearing preservation can be maximized.

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Compliance with ethical standards

Conflict of interest All authors that they have no conflict of interest.

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