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Stereotactic radiotherapy in acoustic neuroma cases: Tumor control and clinical results

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Abstract

Since acoustic neuromas (AN) are slow-growing tumors, they frequently reduce patients' quality of life by compressing adjacent nerves. After evaluating various factors, the most appropriate treatment for the patient is preferred among follow-up, surgery, or radiotherapy. Surgery and radiotherapy have been shown to have comparable results in AN. Stereotactic radiotherapy (SRT) has long emerged as a viable option for treating intracranial tumors. Thus, it was aimed to determine the local control rate (LCR), and treatment failure and to evaluate the hearing level and facial nerve symptoms in AN treated with SRT. Forty-five patients were treated consecutively with CyberKnife-SRT between January 2014 and December 2021. Tumors were anatomically classified according to Koos grade; patients presenting with hearing impairment were graded according to the Gardner-Robertson (GR) scale and patients' expressions. Loss of function in the facial nerve was also evaluated according to the House-Brackman scale. SRT was applied to 24 patients with 12 Gy/1 fx, 18 with 18 Gy/3 fx, and 3 with 25 Gy/5 fx. At a median follow-up of 24 months (2-73), progression was detected in 4 (8.9%) patients. None required additional intervention, and no treatment failure was observed (0%). Tumor control was achieved in 91.1% of the patients; 2-y and 5-y LCR were 91.2% and 79.8%. It was observed that 3 (30%) out of 10 patients who had serviceable hearing according to the GR scale at the beginning were non-serviceable hearing during the follow-up. Transient facial paralysis was observed in 3 (6.7%) patients. No statistically significant factor could be detected in LCR, hearing, and facial nerve preservation. Our findings are similar to previous SRT data regarding LCR, treatment failure, hearing preservation, and facial nerve impairment. SRT is an effective treatment method for AN with reasonable results.

Keywords: Acoustic neuroma, facial nerve impairment, hearing preservation, local control rate, stereotactic radiotherapy

Introduction

Acoustic neuromas (AN) are benign brain tumors arising from the myelin sheath of the vestibulocochlear nerve and constitute 6-8% of intracranial tumors [1]. Since they are slow-growing tumors, they frequently reduce patients' quality of life by compressing adjacent nerves. Most patients exhibit unilateral hearing loss, tinnitus, ataxia, vertigo, changes in facial feeling, and headaches [2]. However, modern imaging techniques can incidentally identify AN before they manifest symptoms.

The treatment options are quite broad. In asymptomatic cases detected incidentally, follow-up may be an alternative to surgery and radiotherapy, the most frequently utilized treatment modalities [3]. Various factors such as age, comorbidities, tumor size, location, symptoms, and patient desire are evaluated to select the best treatment option. Small asymptomatic tumors are typically managed conservatively, and routine follow-up includes audiometry and magnetic resonance imaging (MRI) [4]. Treatment with microsurgery or radiotherapy is considered if the AN patient exhibits symptoms of growth or in the event of neurological impairment. Microsurgery is the treatment of choice for patients with larger tumors or symptoms related to

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brain stem compression. Permanent hearing loss and facial paralysis risk due to facial nerve injury are observed at a high rate with surgical treatment [5]. In this context, radiotherapy may be preferred because of the difficulty of surgical treatment and the complications that may develop. Microsurgery and radiotherapy have been shown to have comparable progression-free survival statistics in numerous case series, and this finding has been confirmed in several reviews [6-9].

Stereotactic radiosurgery and/or radiotherapy (SRS, SRT) has emerged as a viable option in intracranial tumor management, thanks to modern radiotherapy techniques, targeting the tumor with high sensitivity and protecting critical structures better. Stereotactic techniques were used for the first time in the treatment of AN in 1979. Then they started to be applied in treating AN, especially in small tumors that tend to grow [8-10]. On the other hand, conventional fractionated stereotactic radiotherapy (FSRT) techniques have been involved in the treatment of AN for a long time. In terms of the efficacy of these radiotherapy techniques, numerous studies have demonstrated that SRT and conventional FSRT have tolerable toxicity and satisfactory tumor control rates for treating AN [3].

Reliable and effective results of stereotactic methods have been reported in many studies [11-14]. In this context, we thought to present our experience of our clinic to the literature by evaluating both tumor control and clinical results in AN cases treated with SRT, which has been applied in our clinic since 2014. In our study, we aimed to determine the local control rate (LCR), treatment failure rate and to evaluate the hearing level and facial nerve symptoms in treated cases.

Material and Methods

The study was carried out with the permission of the Samsun University Clinical Researches Ethics Committee (Date: 9.11.2022, Decision No: 11/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki [18]. Individual approval was waived due to retrospective design.

We retrospectively analyzed patients with AN who were treated with CyberKnife® (Accuray, Sunnyvale, USA) SRT (CK-SRT) in the Radiation Oncology Clinic of Samsun Training and Research Hospital between January 2014 and December 2021. Patients meeting the inclusion criteria were required to be older than 18 years of age, diagnosed with AN as determined by imaging, or diagnosed with pathological AN. Patients who received more than five fractions for SRT or received conventional FSRT were excluded.

The patient's clinical data, including demographic information and outcomes, were collected from the patient's medical records. Both tumor characteristics (size, volume, proximity to critical structures) and treatment parameters (dose, number of fractions) that may affect response to treatment were recorded in detail. Tumors were anatomically classified according to the Koos grading system [15], and hearing loss in patients presenting with hearing impairment was graded according to the Gardner-Robertson (GR) scale [16]. The loss of facial nerve function during the follow-up period was also evaluated and recorded according to the House-Brackman scoring system [17].

Treatment

Treatment decision was made after a multidisciplinary tumor board evaluated each patient's symptoms, medical condition, and disease characteristics. Additionally, the patient's desire significantly influenced the treatment option. Radiosurgery was performed using the CK robotic radiosurgery system.

All patients were simulated in the supine position and immobilized by a thermoplastic mask. Computed tomography simulations were done with a slice thickness of 1 mm. T1-weighted MRI with gadolinium contrast, 1 mm thick, was taken to be used for fusion. The CT and MRI were registered in the treatment planning system, and the tumor was delineated after fusion. A contrast-enhanced mass was defined as gross tumor volume (GTV). The planning target volume was defined as GTV in most patients, and a 1 mm margin was added to the GTV in some. Treatment was administered in single or multiple (3 or 5) fractions according to target volume and proximity to prominent structures. The biologically effective dose (BED3) calculated using $\alpha/\beta=3$ for tumor effects was used to compare treatment response.

Clinical and radiographic follow-up

The first clinical evaluation of the patients was performed one month after SRT, and the first radiological evaluation 3 months later. Subsequently, clinical and radiological evaluation was performed every 6 months and then annually.

Endpoints and statistical analysis

Primary endpoints were LCR and treatment failure ratio, and secondary endpoints were hearing and facial outcomes. According to the results of the MRI, local control was described as a stable disease or a partial response. 2 mm increase in tumor size and persistence of the increase in follow-up were considered as progression [18]. Transient enlargements were considered pseudoprogression. Treatment failure was defined as leading to a new intervention, such as re-irradiation or surgery, in progressed patients.

According to the GR scale, if there was no change in grade, the hearing outcome was classified as stable; otherwise, it was classified as worse if there was a decline in grade. In addition, following SRT, a hearing function was assessed based on serviceability (i.e., serviceable/non-serviceable). No hearing loss, normal hearing, the ability to use a phone, and GR grade I or II were all considered to be indicators of hearing serviceability. However, GR grade III or IV, no functional hearing, and inability to use the phone were all deemed non-serviceable hearing [18]. Any new onset or progression of prior facial paralysis or loss of sensation was referred to as facial nerve impairment.

After testing the data for normality with the Shapiro–Wilk test, continuous variables were shown as medians and categorical variables as frequency and percentage (%). The groups were compared using the chi-square test, factors affecting treatment

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response were compared with independent groups t-test for normally distributed data. LCR was estimated using the Kaplan-Meier technique. Differences were analyzed with the log-rank test. Data statistical analysis was processed using IBM SPSS statistical software (version V25.0; IBM Corporation, Armonk, NY, USA). All tests were 2-sided, and p values <0.05 were considered statistically significant.

Results

The characteristics of the patients and tumors are summarized in Table 1. The median age of the patients was 53 (27-75), 23 women and 22 men. The most common complaints of the patients were hearing loss (65.9%), tinnitus (65.9%), and dizziness (27.9%). Two patients had been operated on before and were included in the SRT program for recurrent disease.

Table 1. Patient and treatment characteristics

Variable	N (%)	Median (range)
Age		53 (27-75)
Gender		
Female	23 (51.1)	
Male	22 (48.9)	
Symptoms*		
Hearing loss	29 (65.9)	
Tinnitus	29 (65.9)	
Dizziness	12 (27.9)	
Headache	10 (23.3)	
Radiosurgery indication		
Primary (Image-diagnosed)	43 (95.5)	
Recurrence	2 (4.5)	
Size of tumor (cm)		1.6 (0.5-3.5)
Volume of tumor (cc)		2.04 (0.1-7.97)
Koos grade		
1	7 (15.6)	
2	10 (22.2)	
3	22 (48.9)	
4	6 (13.3)	
Gardner Robertson scale		
1	5 (16.1)	
2	10 (32.3)	
3	11 (35.5)	
4	1 (3.2)	
5	4 (12.9)	
Radiotherapy		
SRS	24 (53.5)	
SRT	21 (46.5)	
RT dose (Gy)		
12	24 (53.5)	
18	18 (40)	
25	3 (6.7)	
RT fraction		
1	24 (53.5)	
3	18 (40)	
5	3 (6.7)	
Coverage		97 (85-99.5)
BED3		
54 Gy	18 (40)	
60 Gy	24 (53.5)	
67.7 Gy	3 (6.7)	

BED: biologically effective dose, RT: radiotherapy, SRS: stereotactic radiosurgery, SRT: stereotactic radiotherapy
* Some symptoms were observed together

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The median tumor size was 16.1 mm (5-35), and the tumor volume was 2.04 cc (0.11-7.97). According to the Koos grading scale, seven patients scored 1, 10 scored 2, 22 scored 3, and 6 scored 4. While SRT was administered at a dose of 12 Gy/fx to 24 patients, 18 Gy/3 fx SRT was applied to 18 patients, and 25 Gy/5, fx SRT, was applied to 3 patients.

At a median follow-up of 24 months (2-73), partial response was observed in 19 (42.2%) patients, stable disease was observed in 22 (48.9%) patients, and progression was detected in 4 (8.9%) patients. Pseudoprogression was observed in 14 of the patients in the first two years.

Tumor control was achieved in 91.1% of the patients; 2-y and 5-y LCR were 91.2% and 79.8% (Figures 1 and 2). In terms of local control, there was no difference in the application of SRT in a single or multiple fractions (P=.343). No statistically significant factor on LCR could be detected in the univariate analysis (Table 2). A reduction in tumor size was observed at 3 to 5 years (Figure 3). Progression was observed at a median of 21 (6-60) months. None of them required additional new intervention. No treatment failure was observed (0%). In the subgroup analysis, 26 patients with 24-month follow-up were re-evaluated, with 2-y and 5-y LCRs of 100% and 88.9%.

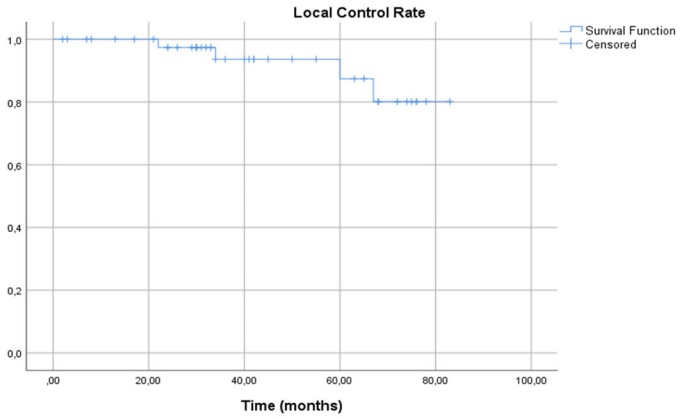

Figure 1. Kaplan-Meier graph of local control rates

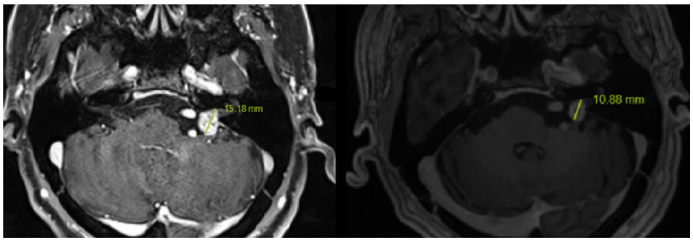

Figure 2. Partial tumor response in magnetic resonance imaging taken before treatment and during the 24-month follow-up period of a patient who underwent SRT at 12 Gy/1 fraction

Table 2. Local control rates in univariate analysis

Factors	n	Mean	HR (CI, 95%)	2-y	5-y	p
Age						.611
<55	26	76.01	3.62 (68.91-83.11)	100	84.7	
≥55	19	74.26	3.60 (67.19-81.33)	93.3	93.3	
Gender						.613
Female	23	77.84	3.60 (70.78-84.91)	100	92.4	
Male	22	74.26	3.70 (61.96-76.47)	94.4	75.6	
Koos grade						.928
1-2	17	70.53	4.88 (60.95-80.11)	93.3	84.8	
3-4	28	77.79	3.19 (71.53-84.04)	100	87.5	
Tumor size						.059
<1 cm	7	76.68	2.27 (75.23-84.13)	96.9	96.9	
≥1 cm	38	64.4	7.84 (49.02-79.77)	100	53.3	
Tumor volume						.134
<1	23	81.22	1.67 (77.47-84.50)	100	100	
≥1	22	68.52	4.79 (59.19-77.97)	95	69.7	
Proximity to the cochlea						.161
Yes	32	-	-	96.9	96.9	
No	13	-	-	100	53.3	
Radiotherapy						.343
SRS	24	66.43	3.76 (59.05-73.80)	95.5	86.8	
SRT	21	79.88	2.04 (75.88-83.89)	100	92.3	
Coverage						.256
<96%	15	69.20	5.44 (58.53-79.88)	91.7	68.8	
≥96%	30	78.90	2.82 (73.37-84.43)	100	94.7	
BED3						.554
54 Gy	18	-	-	100	90.9	
60 Gy	24	-	-	95.5	86.8	
67.7 Gy	3	-	-	100	100	

BED: biologically effective dose, CI: confidence interval, HR: hazard ratio, SRS: stereotactic radiosurgery, SRT: stereotactic radiotherapy

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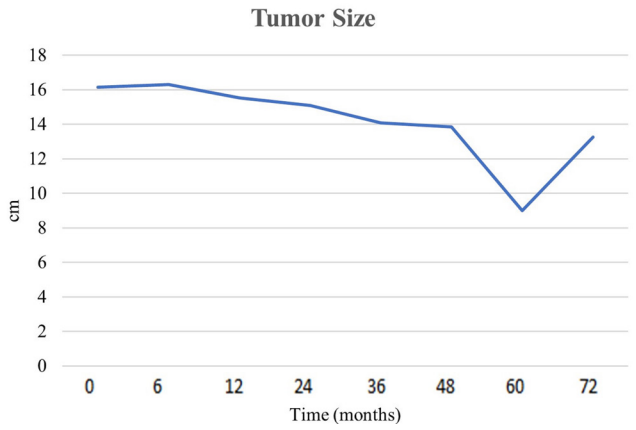

Figure 3. Graph of tumor size reduction over time during follow-up

In the entire cohort, symptoms regressed in 10 (22.1%) patients, remained unchanged in 31 (64.4%) patients, worsened in 4 (8.9%) patients, and were unknown in 2 (4.4%) patients at the end of the follow-up. Six of 29 patients who presented with the complaint of hearing loss did not have an audiogram examination at the time of initial diagnosis. In the follow-up period, only 7 patients were examined by an audiogram, and symptom evaluations were made subjectively according to the patient's expression. When the hearing of 29 patients who presented with hearing complaints was re-evaluated, it was found that the hearing of 6 (20.6%) patients had improved, 17 (58.6%) had no change, 4 (13.8%) had worsened, and 2 (6.9%) patients' hearing was unknown. It was observed that 3 (30%) out of 10 patients who had serviceable hearing according to the GR scale at the beginning were non-serviceable hearing during the follow-up period. There was no difference in hearing preservation between single-fraction or multiple-fraction SRT (P=.875). No statistically significant factor could be detected in hearing preservation, including cochlear Dmax and Dmean values (Table 3, P=.578, P=.283).

Transient facial paralysis was observed in 3 (6.7%) patients within the first 6 months. It was seen 3 months after SRT in 2 of these patients (House-Brackmann grade 4) and 15 days after SRT in 1 (House-Brackmann grade 5). After medical treatment, symptoms resolved completely in 3 patients. There was no difference in age (P=.201), gender (P=.590), Koos grade (P=.568), proximity to the cochlea (P=.828), tumor size (P=.631), radiotherapy (P=.635), BED (P=.175), cochlea Dmax (P=.813), and Dmean (P=.500) values in patients with facial paralysis.

Table 3. Demographic and clinical characteristics of patients with hearing preservation

Characteristic	Stable/improved hearing	Worsened hearing	p
Age	55.65+/-7.82	47.01+/-15.85	.248
Gender			.552
Female	11 (84.6)	2 (15.4)	
Male	14 (87.5)	2 (12.5)	
Radiotherapy			.875
SRS	16 (84.2)	3 (15.8)	
SRT	9 (90)	1 (10)	
Koos grade			.568
1-2	7 (77.8)	2 (22.7)	
3-4	18 (90)	2 (10)	
Tumor size (cm)	1.65+/-0.72	1.25+/-0.55	.250
Tumor volume (cc)	2.09+/-6.49	2.51+/-2.49	.875
Proximity to the cochlea			.552
Yes	17 (81)	4 (19)	
No	8 (100)	0 (0)	
Cochlea Dmax (cGy)	1300+/-472	1409+/-242	.578
Cochlea Dmean (cGy)	776+/-432	1090+/-236	.283
Coverage (%)	98+/-0.2	96.83+/-1.49	.197
BED3			.821
54 Gy	7 (87.5)	1 (12.5)	
60 Gy	16 (84.2)	3 (15.8)	
67.7 Gy	2 (100)	0 (0)	

BED: biologically effective dose, SRS: stereotactic radiosurgery, SRT: stereotactic radiotherapy

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Discussion

Owing to their effective tumor control, hearing preservation, and improvement of existing symptoms without operation risk, the latest evidence suggests that SRT should be considered an alternative AN therapy [3,10-14,18]. Upon this background, our analysis sought to determine if SRT could accomplish these objectives. During our follow-up period, none of the patients who underwent SRT required additional tumor treatment. 30% of individuals, which is comparable to other research, lost functional hearing. Our findings suggest that treating AN with SRT provides remarkable tumor control with a negligible rate of neurological morbidity.

Excellent local tumor control has been reported in patients undergoing SRT to date. SRT can be delivered using the Gamma Knife (GK), CK, or Linear Accelerator. Most of the information that guided AN management came from the data, including GK-SRT results. Their 5-y LCR have been reported to be 90% and higher [3]. Comparable results were obtained with the CK-SRT. In the series of 119 patients who underwent CK-SRT with a median follow-up of 49 months, 3-y and 5-y LCR were reported as 94% and 88% [19]. In the Stanford University experience of 383 patients treated with CK-SRT, the 3-y and 5-y LCR were 99% and 96%, respectively [20]. In a meta-analysis published in 2017, the mean LCR was 96.3%, according to the results of 11 studies involving 800 patients in which CK-SRT was applied [21]. In another recently published study examining 123 patients who underwent CK-SRT with a median extended follow-up of 6 years, 5-y, and 8-y progression-free survival was reported to be 96% and 92% [22]. In light of these studies, it is possible to say that there are similar and excellent LCR in terms of both GK and CK-based radiosurgery.

Various studies have documented the transient enlargement of AN, known as 'pseudo-progression' within three years after radiosurgery, which occurs in 30% [3,23,24]. Unfortunately, pseudoprogression makes evaluating treatment responses more challenging. Studies where pseudoprogression has been reported, vary as to which values are considered pseudoprogression [25]. Rueb et al. [25] proposed a new definition for response criteria in their study, in which they categorized pseudoprogression as early (<12 months) and late (≥12 months). This study defined pseudoprogression as an increase in volume >20% above baseline followed by a decrease in volume within 24–36 months; progression was defined as an increase in volume ≥40% above baseline. In our study, pseudoprogression was observed in 14 patients in the first two years; except for these patients, progression was detected in 2 patients at 30-month and 60-month follow-ups. The other two patients considered as progression were those with a last follow-up period of 6 months and 12 months. However, since the follow-up period was short in these 2 patients, it should be kept in mind that these patients may not actually progress, and these growths may be pseudoprogression. Therefore, when we re-evaluated 26 patients with 24-month follow-up, 2-y and 5-y LCR were 100% and 88.9%.

Furthermore, several studies mention treatment failure ratios as well as LCR. It has been observed that this terminology is used when a new intervention, such as surgery or re-irradiation, is required for the progressive disease. For instance, in a study of 119 AN cases who underwent CK-SRT, only nine required surgery, although tumor growth was detected radiologically in 19 patients. They were considered treatment failure [19]. In our study, none of the patients with progression required additional new interventions; therefore, treatment failure was not observed (0%).

According to previous data, some factors have been identified in achieving tumor control. Klijn et al. [26] reported that tumor control was associated with tumor size in a series of 420 patients. It was determined that 94.1% of tumors below 0.5 cc decreased to 80.7% in tumors over 6 cc. In the Stanford University experience, while 5-y LCR was 98% in patients with tumor volume <3.4 cc, the ratio decreased to 89% in patients larger than >3.4 cc [20]. The same group also investigated the effect of neurofibromatosis type 2 on outcomes, reporting worse LCR in neurofibromatosis type-2 related tumors compared to sporadic ones (5-y LCR 84% vs. 96%). In contrast to numerous research, we did not discover any patient- or tumor-related variables that predict tumor control, similar to Przybylowski et al. [19]. In addition, statistical analysis could not be performed because one patient was known to have neurofibromatosis type 2 in the entire cohort in our study.

Another essential objective in the management of AN is hearing preservation. To the best of our knowledge, it has been shown in numerous studies to date that time elapsed after SRT, cochlea doses, age, baseline hearing function, and classification of Koos are associated with worsening hearing [3,27]. According to the meta-analysis results, which included more than 4000 patients who underwent GK-SRT, hearing preservation was found to be 51% 3-4 years after the treatment [28]. Tamura et al. [29] suggested that serviceable hearing can be preserved in patients with good hearing function at the beginning, under the age of 50, and whose cochlea dose did not exceed 4 Gy. Hearing protection was reported to be over 50% in CK SRT studies [19,21,22]. However, these results may be misleading due to the small number of patients, the relatively small tumor diameter, and the inadequacy of audiogram examinations. In our study, the serviceable hearing was preserved at a rate of 70%, and no correlation was found with factors such as cochlea dose, tumor diameter, and age. However, it should be noted that in our study, audiogram analysis was not performed in most of the patients during the follow-up period, and hearing assessment was often performed based on patient statements.

In cases of AN, facial and trigeminal nerve damage and related symptoms may occur due to the crucial location. Damage to these nerves after SRT can inevitably be observed due to the close relationship. In addition, the severity of complaints may increase as a consequence of edema that develops, especially in larger tumors after SRT. While the rates of facial nerve damage are 0% to 8% with CK-SRT, these rates are 0% to 10% for GK-

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SRT [30,31]. Our study found that there was temporary facial paralysis at a rate of 6.6%.

Fractionated treatments can provide radiobiological tissue repair has led to a tendency to use multifractional treatments to protect sensitive structures in the vicinity due to their critical location in AN cases. According to non-randomized studies, although some research suggests that multifractionated therapies cause fewer complications, other studies suggest that single-fractionated treatments have fewer adverse effects [3,21,30,32]. In the review evaluating the results of 12 SRT and 2 FSRT studies, treatment failure rates were similar, and hearing impairment was higher in the SRT studies than in the FSRT [32]. When SRT and FSRT were compared in terms of facial nerve deterioration, rates of 3.6% and 11.2% were reported. Another study found no difference in facial nerve deterioration in AN cases treated with either SRT or Linear Accelerator based hypofractionated treatment [13]. Studies comparing SRT with conventionally FSRT yield mixed results, while studies comparing SRT and hypofractionated FSRT have not found a statistical difference between outcomes. In the series we presented, approximately half of the patients underwent SRT, and the remaining half underwent hypofractionated SRT. There was no difference in either LCR and hearing and facial nerve results.

There were some limitations in this study. First, the study's retrospective nature entails known restrictions on the collection and accuracy of the data. It can be challenging to quantify and objectively evaluate subjective symptoms like tinnitus and vertigo during routine follow-up. Another related limitation is that assessment of hearing preservation is often based on patient statements, with insufficient audiogram examinations during follow-up. Neurofibromatosis status of the patients was also not evaluated, one patient was known to have neurofibromatosis type 2 in the entire cohort in our study.

Conclusion

Our findings are similar to previous SRT data in terms of LCR, treatment failure rate, hearing preservation rates, and facial nerve impairment. However, we did not discover any patient- or tumor-related variables that predict either tumor control or hearing and facial nerve results. SRT is an effective treatment method in the treatment of AN with reasonable results regarding hearing and facial nerve preservation and tumor control.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was initiated with the approval of the Samsun University Clinical Research Ethics Committee (Date: 9.11.2022, Decision No:11/8).

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