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ORIGINAL ARTICLE

The Role of Radiotherapy in Vestibular Schwannoma's Treatment: Retrospective Trial

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OBJECTIVE

This retrospective study, spanning from 2012 to 2022 at Dokuz Eylul University Radiation Oncology Institution, aims to analyze outcomes in vestibular schwannoma (VS) patients undergoing various treatments.

METHODS

Thirty-two adult patients (≥18 years) who received stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT), or fractionated radiotherapy (FRT) at DEU and had a minimum follow-up of six months were included. The Koos Grading Scale for VS lesions, Gardner-Robertson Grading for hearing, and House-Brackmann Scale for facial nerve functions were used. Statistical analyses employed SPSS v24, Kaplan-Meier methodology, and the log-rank test.

RESULTS

The median age of the patients was 56, predominantly exhibiting Koos 4 lesions (43.8%). The median VS volume was 3.5 cm^3, and the Planned Target Volume (PTV) was 5.4 cm^3. Common fractionation schemes were 5×4.5/5 Gy (46.9%) and 1×12/13 Gy (43.8%). At two years, overall survival (OS) reached 96.9%, with lesion stability in 46.9% and regression in 53.1%.

CONCLUSION

This study underscores the importance of considering treatment fractionation, cochlear sparing, and lesion grading to achieve favorable outcomes and effectively manage toxicity in patients with vestibular schwannomas (VS). The Koos score has been identified as a significant factor influencing lesion regression. Further investigation involving a larger patient number is recommended to delineate the factors influencing treatment response.

Keywords: Progression-free survival; stereotactic radio therapy; vestibular schwannoma.

INTRODUCTION

Vestibular schwannoma (VS) is a benign tumor originating from Schwann cells of the vestibulocochlear nerve. The global incidence of VS, as revealed by a systematic review, ranges from 3 to 5.2 per 100,000 individuals. While the average onset age is typically 60 years, our study demonstrates a slightly younger

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average age of 53 years. Notably, VS diagnosis is more common among individuals aged 70 years and older. Furthermore, there is no significant difference in incidence between genders,[1,2] although our study found a slightly higher prevalence among males, with 56.2% compared to 43.8% among females. VS can be categorized into three groups: homogeneous VS, heterogeneous VS, and cystic VS. Notably, cystic VS is considered more aggressive than the solid type.[3] The most frequently observed symptoms of VS include progressive or sudden hearing loss (94%), persistent unilateral tinnitus (83%), and vertigo (61%). Less common symptoms include imbalance, facial and trigeminal neuropathy, headache, hydrocephalus, and brainstem compression-related symptoms.[4–6] Our study findings align with these observations. Given its benign nature, the primary objective of VS treatment is to achieve local control while preserving nerve functions. Treatment modalities, such as observation, surgery, and radiation therapy (RT), are selected based on various factors, including patient age, tumor size, growth rate, symptomatology at diagnosis, and patient preferences.[5–7] Observation is a viable option for small, asymptomatic, incidentally diagnosed tumors. A systematic review, which compiled data from 3,652 patients across 26 studies, revealed that hearing loss progression during observation for sporadic VS patients follows a consistent pattern, with approximately 75% of patients retaining serviceable hearing (SH) at 3 years, 60% at 5 years, and 40% at 10 years.[5,8] Surgery is the preferred treatment for large (>3 cm) and giant (>4 cm) VS.[9] Various classification scales, with the Koos grading scale being the most commonly used, categorize schwannomas into four distinct categories.[4] Koos 4 lesions can be life-threatening, necessitating surgery,[5] with associated mortality rates of approximately 0.38% and complication rates of 5.3%.[10] Stereotactic radiosurgery (SRS) is a single-fraction radiation therapy technique employed for the treatment of intracranial lesions. It involves the use of a stereotactic apparatus and narrow multiple beams to deliver a high therapeutic dose to a precisely defined treatment volume while minimizing radiation exposure to surrounding normal brain tissue. SRS offers an effective alternative to surgery. The same technique, when used for delivering multiple dose fractions to an intracranial lesion, is called stereotactic radiotherapy (SRT).[11–13] Fractionated RT (FRT) and SRS exhibit no significant differences in local control and toxicity profiles. SRS typically prescribes doses of 12–13 Gy, whereas FRT employs doses ranging from 45–57.6 Gy. For SRT, 4–5 Gy in 5 fractions is standard. SRS is favored for smaller lesions, while fractionated therapy is recommended for larger lesions (Koos 3–4).[14–21] In this retrospective trial, our aim is to investigate local control rates and toxicity profiles in patients treated with SRS, SRT, and FRT using linear accelerator (LINAC)-based machines. We seek to compare our findings with results from existing studies in the literature and evaluate the effectiveness and side effects of SRS/SRT using flattening filter-free (FFF) energy beams.

MATERIALS AND METHODS

Between 2012 and 2022, we treated 32 patients with vestibular schwannoma (VS) at Dokuz Eylul University (DEU) Radiation Oncology Institution. The inclusion criteria encompassed patients aged 18 and above who received SRS, SRT, or FRT at our institution and were followed for a minimum of six months. Conversely, patients who were below 18 years of age, those with neurofibromatosis type 2, or those treated elsewhere were excluded from the study. The retrospective analysis of patient data was conducted utilizing the DEU Radiation Oncology Archive. VS lesions were graded using the Koos grading scale. The assessment of patients' hearing was performed in accordance with the Gardner-Robertson Grading classification, and facial nerve function was evaluated using the House-Brackmann scale. Treatment efficacy and toxicity were assessed through follow-up examinations, audiometry, and magnetic resonance imaging (MRI) conducted at 6, 12, 18, and 24 months post-radiation. Stable or regressing tumor sizes indicated a positive response to treatment. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24. Overall survival (OS) was calculated taking into account the time from diagnosis. Response and progression-free survival (PFS) analyses were initiated from the first day of radiotherapy (RT). The Kaplan-Meier methodology was employed for treatment response and survival analyses. Factors influencing PFS and treatment response were examined using the log-rank test and the Cox Regression method.

RESULTS

Patient Characteristics

In this retrospective study, we reviewed the medical records of 32 patients who met our inclusion criteria. The median age was 56 years (range: 18–73), with 14 fe-

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male (43.75%) and 18 male (56.25%) patients. The median follow-up duration was 27 months, with a range of 6 to 95 months. Hearing loss was the most common initial symptom observed in 75% of patients, with the majority having serviceable hearing (Gardner-Robertson grade I-II). Other common initial symptoms included tinnitus (50%), imbalance (28.12%), vertigo (25%), and headache (21.87%). Additionally, trigeminal neuropathy (3.12%) and facial neuropathy (3.12%) were among the initial symptoms leading to diagnosis. The majority of VS were classified as Koos 4 (43.8%), followed by Koos grade 2 (31.25%). Refer to Table 1 for a summary of patient characteristics.

These characteristics provide an overview of the patient population and tumor profiles included in the study.

Treatment Characteristics

Patients were immobilized using thermoplastic IMRT head masks. Lesions were delineated on CT simulation scans fused with diagnostic MRI to create the Gross Target Volume (GTV) using Eclipse v15 and Velocity v3.2.1. The Planning Target Volume (PTV) was established by applying a 1 mm margin to the GTV. Organs at Risk (OAR), including the brain, brainstem, medulla spinalis, cochlea, lenses, orbit, chiasma opticum, and optic nerves, were delineated. Figures 1, 2, 3, and 4 illustrate an example of delineated target volumes and OAR for a patient with Koos 4 VS. All treatment plans were developed using Volumetric Modulated Arc Therapy (VMAT) and implemented using TrueBeam STx. Image-Guided Radiation Therapy (IGRT) was employed for all patients during treatment. The median volume of VS was 3.5 cm^3 (range: 0.2 to 26.9 cm^3) and the median Planned Target Volume (PTV) was 5.4 cm^3 (range: 0.6 to 34.8 cm^3).

Tables 2, 3 and 4 provide a summary of the dosimetric characteristics of the treatment.

Figure 5 illustrates the 95% isodose distributions in color wash for a patient with Koos 4 VS treated with 5×5 Gy SRT.

Dosimetric Characteristics

Fractionation schemes varied, with 46.9% receiving 5×4.5/5 Gy and 43.8% receiving 1×12/13 Gy. Conventional fractionation was utilized for a smaller proportion of patients, with a prescribed dose of 25–30×1.8/2 Gy (9.3%). Stereotactic radiation treatment (SRS/SRT) utilized flattening filter-free beam energies, specifically 6FFF and 10FFF. Dose variations to the ipsilateral cochlea were observed based on treatment type.

Clinical Outcomes

A comprehensive clinical evaluation, including MRI scans, was conducted at specific intervals post-treatment. Specifically, all 32 patients underwent assessment at the six-month mark, while 20 patients were available for evaluation at the 12-month interval. The 18-month follow-up included 18 patients, and at the 24-month post-treatment mark, 16 patients were assessable. Remarkably, the two-year overall survival (OS) rate was 96.9%, with only one patient succumbing to non-disease-related causes. Disease response showed 46.9% lesion stability and 53.1% regression. No progressions were observed. In terms of symptomatology, 56.3% reported regression, 25% remained stable, and 18.8% experienced progression due to treatment-related toxicities.

Toxicity

Toxicities were categorized as acute and chronic events, with acute toxicity referring to complications occurring within the initial three months post-radiotherapy. Specifically, symptoms such as headache, increased hearing loss according to the Gardner-Robertson (GR) grading system, tinnitus, and vertigo were attributed to pseudoprogression and were encountered in 28.1% of patients. Conversely, chronic toxicity, defined as complications emerging three months after RT, was identified in 31.3% of patients. Refer to Table 5 for a concise summary of chronic side effects observed in our patient cohort.

Of note, the assessment of hearing loss was conducted by comparing post-treatment Gardner-Robertson (GR) Scale scores with baseline GR scores. Additionally, the presence of facial palsy was assessed according to the House-Brackmann Scale, while radiation necrosis was confirmed by MRI in one patient who had a Koos 4 lesion and was treated with 27×2 Gy (54 Gy) conventional RT.

DISCUSSION

This study conducted a retrospective analysis of linear accelerator (LINAC)-based radiation therapy outcomes in VS patients. Various risk factors have been investigated for VS, including allergies, radiation exposure (average 4.6±1.9 Gy), high noise levels, alcohol consumption, diabetes, and dyslipidemia. There is ongoing debate regarding the relationship between hypertension, mobile phone use, and VS. Interestingly, smoking has been associated with a lower risk of VS.[4,22,23] Although this study did not confirm this due to a limited number of patients. 62.5% of pa-

Table 1 Patients and tumor characteristics

	n	%
Total patients diagnosed with VS	32	
Median follow-up	27 months (range: 6–95 months)	
Karnofsky Perfomance Score (KPS)	80–90	
Sex		
Male	18	56.2
Female	14	43.8
Comorbidity		
Diabetes Mellitus (DM)	2	6.3
Cardiovascular disease	1	3.1
Multiple comorbidities (DM, cardiovascular disease, hypertension, hyperlipidemia)	9	28.1
None	20	62.5
Smoking		
Active smokers	4	12.5
Ex-smokers	3	9.4
Non-smokers	25	78.1
İnitial symptoms		
Hearing loss	24	75
Tinnitus	16	50
İmbalance	9	28.12
Vertigo	8	25
Headache	7	21.87
Trigeminal neuropathy	1	3.12
Facia neuropathy	1	3.12
Duration of symptoms	Median of 24 months (range: 1–108 months)	
Basal Gardner-Robertson scale		
Serviceable (Grade I-II)	9	28.2
Non-serviceable (Grade III-V)	15	46.8
Unknown	8	25
Basal House-Brackmann Score		
Grade I	30	93.8
Grade II	1	3.1
Grade IV	1	3.1
Tumor size	Median of 20 mm (range: 8–39 mm)	
Tumor location		
Right-sided	16	50
Left-sided	16	50
Koos Grading Scale		
Koos 1	2	6.3
Koos 2	10	31.3
Koos 3	6	18.8
Koos 4	14	43.8

VS: Vestibular schwannomas

tients had no comorbidities, while 28.1% had multiple comorbidities such as diabetes, hyperlipidemia, hypertension, and cardiac disease (Fig. 6).

Treatment options for VS included observation, surgery, and radiation therapy (RT). Most patients in this study presented with Koos 4 (43.8%) and Koos 2

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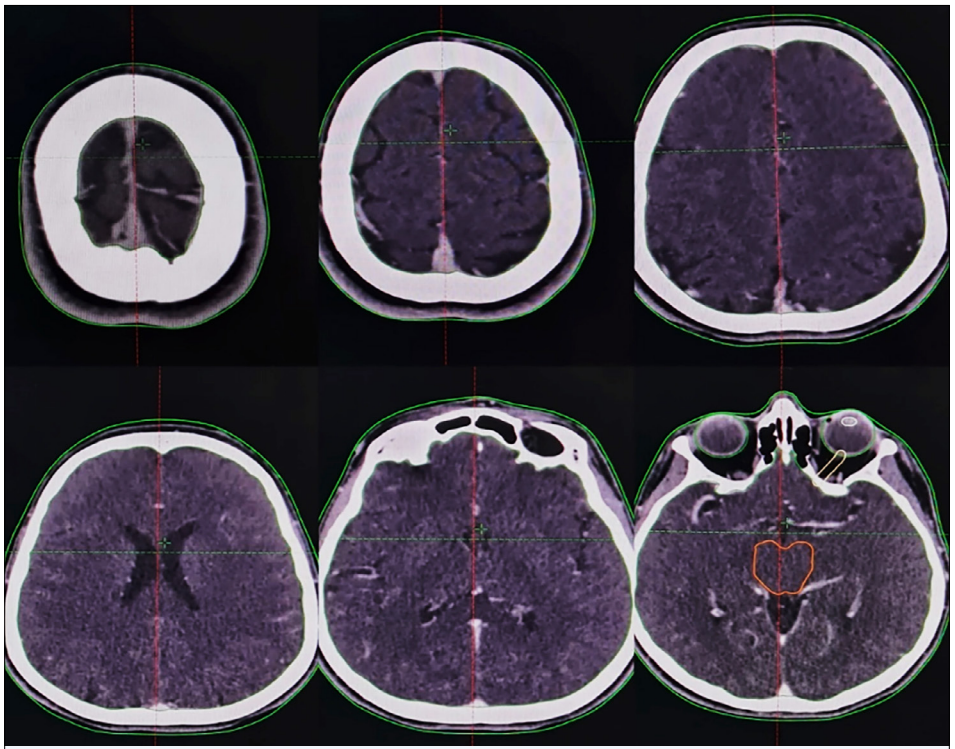

Fig. 1. This figure illustrates an example of delineated Organs at Risk (OAR) for a patient diagnosed with Koos 4 vestibular schwannoma (VS).

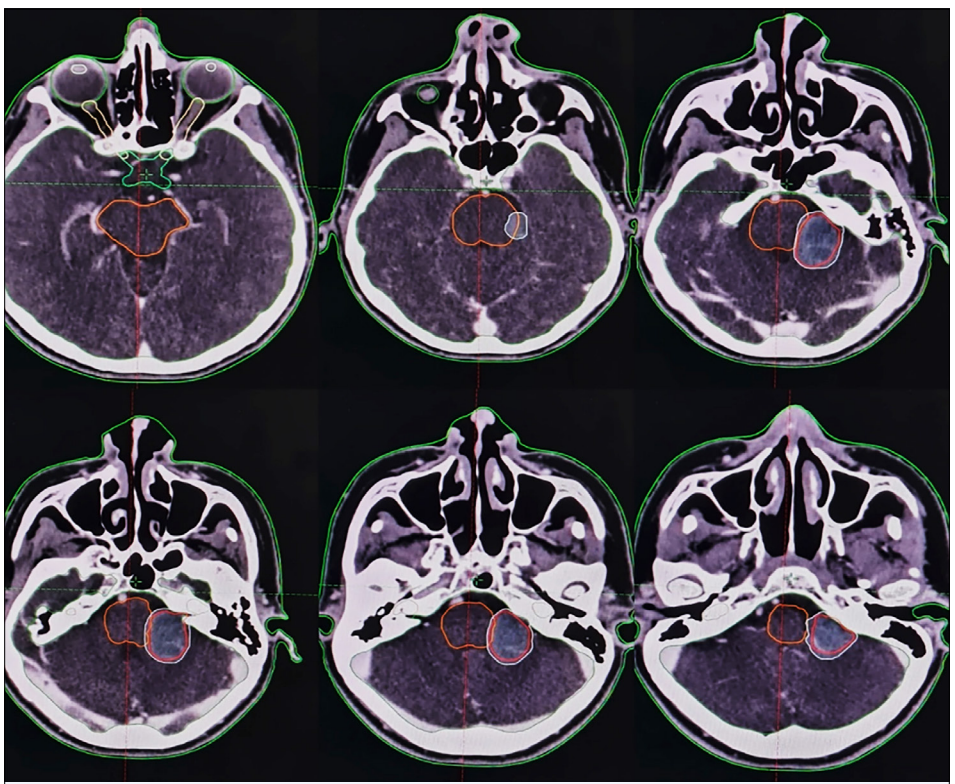

Fig. 2. Depicts delineated target volumes and Organs at Risk (OAR) for the identical patient.

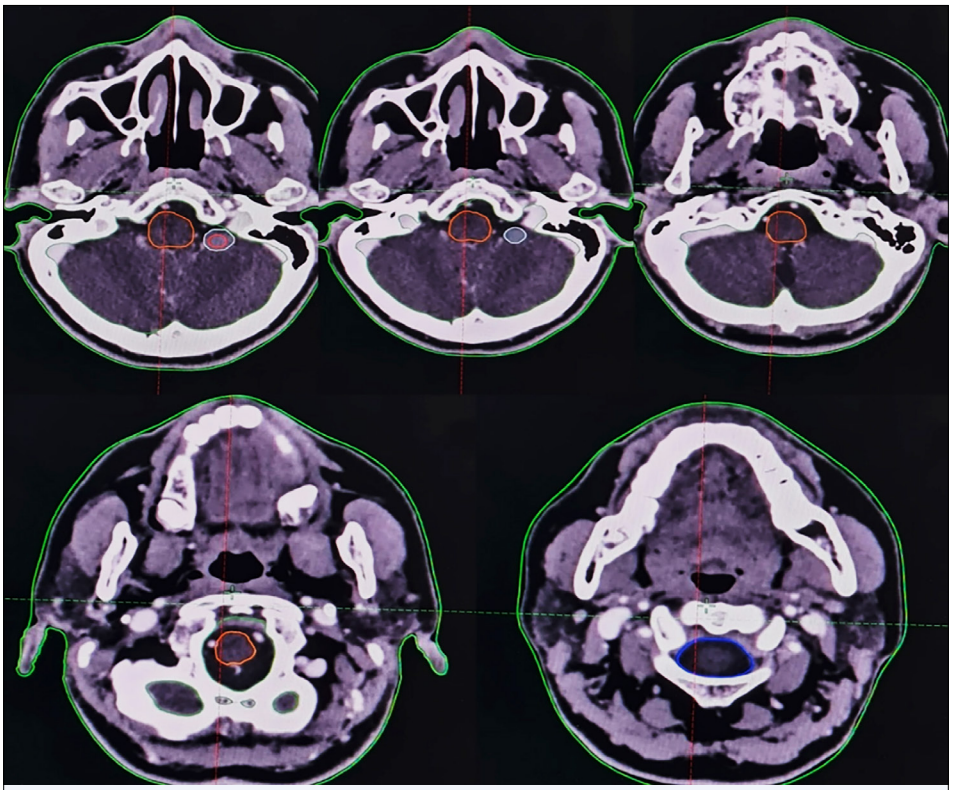

Fig. 3. Continues to illustrate delineated target volumes and Organs at Risk (OAR) for the identical patient.

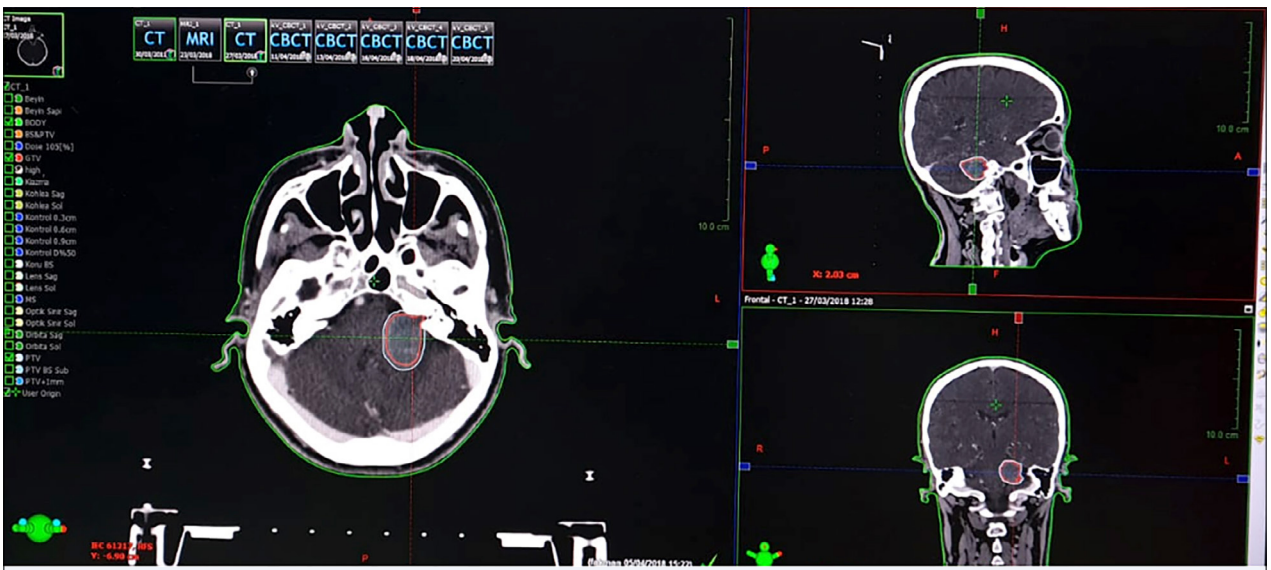

Fig. 4. Depicts an example of delineated target volumes and Organs at Risk (OAR) for the identical patient in axial, sagittal, and coronal sections.

(31.25%) lesions. Long-term observation studies suggest that untreated VS can lead to hearing loss, making interventions like stereotactic radiosurgery (SRS) important for preserving hearing.[24–26] Surgery is typically reserved for large (>3 cm) and giant (>4 cm) VS,[9] while RT is preferred in cases without life-threatening conditions in our center, particularly due to lower rates of facial nerve injury.

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Table 2 Summary of dosimetric characteristics for patients treated with SRS

SRS with 1×12/13 Gy prescribed dose	
Total number of SRS	14 patients (43.8%)
PTV D_{min}	Median 12.1 Gy (94.9% of the prescribed dose)
PTV D_{max}	Median 13.54 Gy (105.7% of the prescribed dose)
D_{mean} of ipsilateral cochlea	Median 11.3 Gy (range: 3.8–13.1 Gy)
D_{max} of ipsilateral cochlea	Median 13.2 Gy (range: 8.7–14.1 Gy)
HI	Median 0.065 (range: 0.04–0.29)
CI	Median 0.56 (range: 0.06–0.85)
GI	Median 9 (range: 3.72–66)

SRS: Stereotactic radiosurgery; PTV: Planned target volume; D_{min}: Minimum dose; D_{max}: Maximum dose; D_{mean}: Mean applied dose; HI: Homogenity Index. Calculated using the formula PTV D_{max}-PTV D_{min}/PTV D_{mean}. CI: Conformity Index. Calculated using the Paddick formula. GI: Gradient Index. Calculated using the formula PIV_{half}/PIV, where PIV is the Prescribed Isodose Volume

Table 3 Summary of dosimetric characteristics for patients treated with SRT

SRT with 5×4.5/5 Gy prescribed dose	
Total number of SRT	15 patients (46.9% of the study population)
PTV D_{min}	Median 21.2 Gy (89.4% of the prescribed dose)
PTV D_{max}	Median 25.42 Gy (106% of the prescribed dose)
D_{mean} of ipsilateral cochlea	Median 18.11 Gy (range: 12.6–24.87 Gy)
D_{max} of ipsilateral cochlea	Median 23.64 Gy (range: 18.96–28.35 Gy)
HI	Median 0.07 (range: 0.05–0.15)
CI	Median 0.76 (range: 0.07–0.89)
GI	Median 5.78 (range: 3.76–56.75)

SRT: Stereotactic radiotherapy

Table 4 Summary of dosimetric characteristics for patients treated with conventional RT

Conventional RT with 25–30×1.8/2 Gy prescribed dose	
Total number of SRS	3 (9.3% of the study population)
PTV D_{min}	Median 47.43 Gy (94.9% of the prescribed dose)
PTV D_{max}	Median 52.16 Gy (104.32% of the prescribed dose)
D_{mean} of ipsilateral cochlea	41.58 Gy
D_{max} of ipsilateral cochlea	50.51 Gy
HI	0.02

RT: Radiation therapy

Radiation therapy is designed to target tumor cells while sparing normal tissues. Stereotactic radiosurgery (SRS) was introduced as an alternative to conventional whole-brain radiation therapy (RT) by Lars Leksell in 1969.[12,27] Treatment fractionation is based on factors such as Koos stage, tumor size, and location, with conventional fractionation preferred for larger lesions and stereotactic radiation therapy with flattening filter-free energies for smaller lesions. Early SRS protocols delivered a single fraction of 20 Gy, which was associated with a notably high toxicity rate (including a 15% incidence of facial nerve injury and a 15% incidence of trigeminal nerve injury). However, in the early 2000s, dose de-escalation studies later revealed that reducing the SRS dose to 12 Gy still maintained similar control rates while significantly reducing the associated toxicity.[13,24,28]

Hasegawa et al.[29] conducted a comprehensive study aimed to determine the long-term survival outcomes of 440 patients diagnosed with VS who underwent gamma knife SRS.[24] The median follow-up duration was 12.5 years. Notably, approximately one-third of the patients received doses exceeding 13 Gy, while the remaining received doses below this threshold. It was observed that patients who received lower doses (<13 Gy) exhibited a 10-year progression-free survival rate of 90%, while those who received higher doses (>13

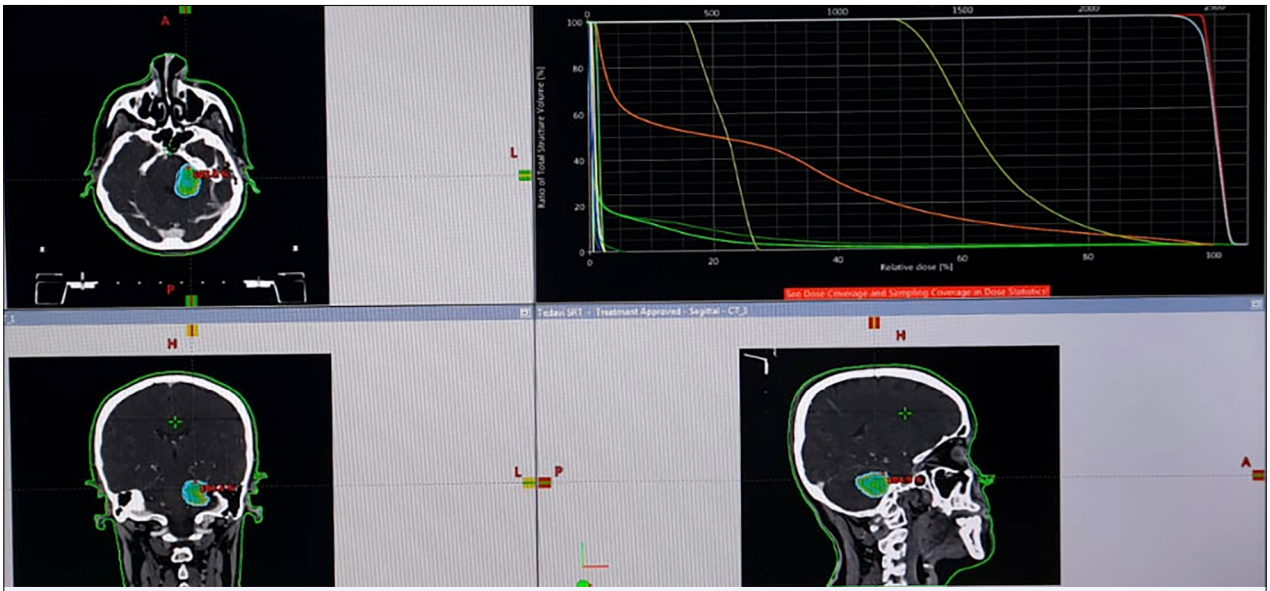

Fig. 5. This figure displays the 95% isodose distributions in color wash and the dose volume histogram (DVH) for a patient with Koos 4 vestibular schwannoma (VS) who underwent treatment with 5x5 Gy Stereotactic Radiotherapy (SRT).

Gy) achieved an even more impressive 96% progression-free survival rate. It is important to note that the administration of lower doses was often associated with larger tumor sizes. Additionally, the study highlighted that toxicity was less prevalent among patients who received lower doses (<13 Gy), further emphasizing the favorable risk-benefit profile of this approach. Furthermore, the research identified tumor volume as a major prognostic factor, underlining its importance in predicting treatment outcomes. In our study, we followed a similar treatment strategy, with 43.8% of our patients receiving 1×12/13 Gy doses for SRS, 46.9% undergoing 5×4.5/5 Gy doses for SRT in, and 9.3% receiving conventional RT with doses ranging from 25–30×1.8/2 Gy.

The significance of dose levels to the cochlea in preserving hearing function has been well-documented in literature. These studies consistently suggest that maintaning an average cochlear dose below 4 Gy is associated with more favorable hearing outcomes.[24,30–32] Schumacher et al.[33] reported that hearing preserving rates reached 100% when the average cochlear dose remained below 6 Gy, whereas rates dropped significantly to 13% when doses exceeded 6 Gy.[24,32] These findings underscore the critical role of minimizing radiation exposure to the cochlea in preserving patients' hearing. In patients who were treated with conventional RT, doses of >60 Gy to the internal auditory canal were linked to 37% incidence of hearing loss, contrasting with a significantly lower 5% rate observed when lower doses were applied.[34,35] Our study found that patients who had SRS with doses <10 Gy to cochlea had better hearing outcomes, while doses >10 Gy were associated with increasing GR scores. However, it is important to note that for patients treated with SRT and convantional RT, our study's dataset was insufficient to establish a clear relationship between dosimetric factors and hearing loss. The evaluation of this relationship was performed using Cox Regression analysis, but due to limited patient numbers, no significant factors were identified, as indicated in Table 6.

In this analysis, it appears that none of the factors reached statistical significance, indicating that there were no significant associations found between these factors and post-treatment hearing loss.

Table 5 A summarized overview of the chronic side effects experienced by our patients

Chronic toxicity	Number of affected patients	%
Hearing loss	6	18.75
Partial hearing loss	3	9.37
Deafness	3	9.37
Trigeminal neuropathy	3	9.37
Facial palcy	3	9.37
HBS grade 2	2	6.25
HBS grade 3	1	3.12
Imbalance	3	9.37
Hydrocephalus	1	3.1
Radiation necrosis	1	3.1

HB: House-Brackmann Scale

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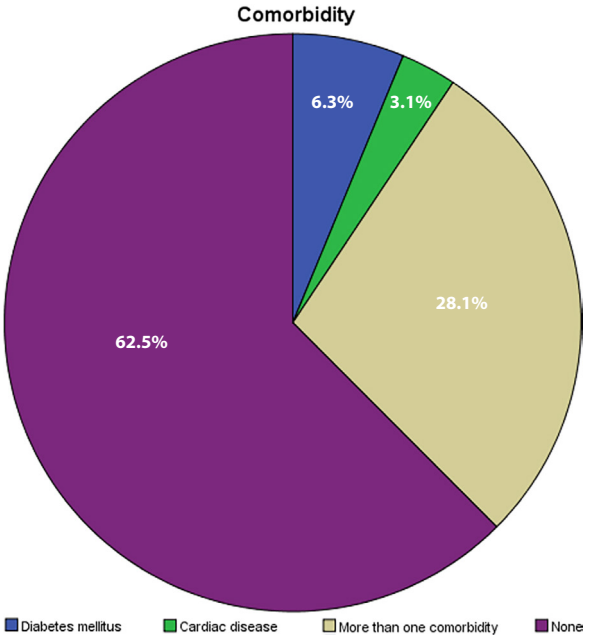

Fig. 6. Comorbidity state of our patients.

Table 7 The results of the Cox Regression analysis aimed at identifying factors that could potentially be associated with post-treatment side effects in patient with VS

Factors that could be associated with side effect	p
Age	0.312
Sex	0.792
Smoking	0.163
Koos grade	0.262
RT dose (Gy)	0.801
Dose per fraction (Gy)	0.861
Fraction number	0.988
PTV D_{mean}	0.710
PTV D_{max}	0.695
CI	0.508
HI	0.350
GI	0.279
Ipsilateral cochlea D_{max}	0.834
Pre-treatment GR	0.280
Pre-treatment facial nerve HBS	0.271

HBS: House-Brackmann Scale

Table 6 Presents the results of the Cox Regression analysis, wich aimed to identify factors associated with post-treatment hearing loss in patients with VS

Associated factors	p
Age	0.951
Sex	0.474
Comorbidity	0.354
Koos grade	0.452
RT dose (Gy)	0.534
Dose per fraction (Gy)	0.767
Number of fraction	0.708
PTV volume	0.775
GTV volume	0.720
PTV D_{mean} (Gy)	0.507
PTV D_{max}	0.526
Ipsilateral cochlea D_{mean} (Gy)	0.928
Ipsilateral cochlea D_{max} (Gy)	0.658
CI	0.983
HI	0.796
GI	0.483
Pre-treatment GR score	0.742

GTV: Gross Target Volume; GR: Gardner-Robertson Grade

Table 8 The results of the Cox Regression analysis conducted to identify factors that could potentially influence the regression of tumors in patients with VS

Factors that could effect tumor's regression	p
Age	0.258
Sex	0.415
Comorbidity	0.660
Smoking	0.970
Koos grade	0.004
RT dose (Gy)	0.605
Fraction per dose (Gy)	0.374
Number of fraction	0.410
PTV volume	0.659
GTV volume	0.809
Energy	0.110
PTV D_{mean} (Gy)	0.726
PTV D_{max} (Gy)	0.660
CI	0.601
HI	0.534
GI	0.775
MU	0.646

MU: Monitor Unit

The study considered stable or regressing lesions as controlled disease. At the end of six months of follow-up for 32 patients, 8 lesions (25%) demonstrated regression, 17 lesions (53.125%) remained stable, and 6 lesions (18.75%) showed progression. After 12 months, we had data for 20 out of 32 patients, with 9 lesions (45%) displaying regression, 9 lesions (45%) stable, and 2 lesions (10%) exhibiting progression. At the 18-month mark, data was available for 18 out of 32 patients. Five lesions (27.78%) exhibited regres-

sion, 13 lesions (72.22%) remained stable, and no progression was observed at this point. For the 24-month follow-up, 16 out of the 32 patients were included, with 9 lesions (56.25%) displaying regression, 7 patients (43.75%) maintaining stability, and no instances of progression noted. Importantly, during the follow-up period, all initially identified cases of progression ultimately regressed, leading us to categorize these lesions as instances of pseudoprogression. Our study demonstrated outstanding results in terms of local control (LC) and (PFS), with both LC and PFS rates reaching 100%, surpassing literature values. We noted an increase in GR score in 6 patients (18.75%). Our study achieved a hearing preservation rate of 81.25%, which notably exceeded the range reported in the existing literature (41–79%). We also observed cases of trigeminal neuropathy in 3 patients (9.37%) and facial neuropathy in 3 patients (9.37%) as well. Fortunately, neuropathies were not severe. Our study demonstrated a trigeminal preservation rate of 90.63%, which was consistent with the range reported in the literature (79–99%). However, our facial nerve preservation rate was slightly lower at 90.63%, compared to the literature's reported range of 95–100%.[5] Despite thorough analysis, our study did not identify any significant association between patient characteristics, treatment factors, and post-treatment toxicity (Table 7).

Our analysis aimed to identify factors that could influence the regression of lesions post-treatment. Among the factors considered, the Koos score emerged as a significant determinant (p=0.004, 95% CI: 0.22–0.786). Specifically, Koos 1–2 lesions demonstrated a 25% regression rate, while Koos 3–4 lesions exhibited a substantially higher regression rate of 70%. However, for other factors such as radiation dose, PTV D_{mean}, and PTV D_{max}, our study did not yield conclusive results due to limited available data (Table 8).

CONCLUSION

This study provides valuable insights into the outcomes and side effects of LINAC-based radiation therapy for VS patients, emphasizing the importance of treatment fractionation, cochlear sparing, and lesion grading in achieving favorable clinical outcomes and managing potential toxicities. Additionally, the Koos score was identified as a significant factor influencing lesion regression. However, larger patient cohorts are needed to further validate these findings and explore additional factors affecting treatment responses.

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (no: 2023/07-22, date: 08/03/2023).

Authorship contributions: Concept – F.C., H.O.Ç.; Design – H.O.Ç., S.Ö.; Supervision – H.O.Ç., S.Ö.; Funding – H.O.Ç., Ş.K.; Materials – S.Ö., N.K., Y.O., E.Ö.; Data collection and/or processing – H.O.Ç., S.Ö.; Data analysis and/or interpretation – H.O.Ç., S.Ö.; Literature search – H.O.Ç., S.Ö.; Writing – H.O.Ç., S.Ö.; Critical review – H.O.Ç., S.Ö.

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