

The Retrospective Evaluation of The Local Tumor Control and Adverse Effects of Treatment in Patients Treated Using Cyberknife Stereotactic Radiotherapy in Vestibular Schwannomas

Vestibüler Schwannomalarda Cyberknife ile Stereotaktik Radyoterapi Uygulanan Hastalarda Lokal Tümör Kontrolünün ve Tedavinin Yan Etkilerinin Retrospektif Olarak Değerlendirilmesi

Tanju Berber¹ , Senar Güneç² , Ferdi Aksaray¹ , Sevil Çağırın Kılçksız³ 

¹Istanbul Okmeydanı Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey

²University of Health Sciences, Clinic of Radiation Oncology, Van, Turkey

³Giresun University Faculty of Medicine, Department of Radiation Oncology, Giresun, Turkey

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ABSTRACT

Objective: Although the most common tumors of the cerebellopontin angle of the vestibular schwannomas (VS) are benign tumors and are rarely fatal due to their localizations, the symptoms of the disease decreases the quality of life. The aim of the present study was to evaluate the local tumor control, hearing functions, and the adverse effects of treatment of radiotherapy using Cyberknife® device which is a recently popular non-invasive procedure causing minimum toxicity in the neighboring tissues with sharp dose decreases in the treatment of patients with VS particularly in intracranial tumors.

Methods: Cyberknife® radiosurgery was administered to 28 patients diagnosed with VS in the present study. The patients were followed-up with routine radiologic screening, audiologic tests, and with the evaluation of the neurologic functions. The study was performed retrospectively, and the data of the patients were obtained from the archive files.

Results: CyberKnife® stereotactic radiotherapy was administered to 28 patients diagnosed with VS. The mean follow-up time was 40.25 months. Local control rate was found as 100% in the follow-ups, the rate of protection of hearing in patients with adequate level of hearing was 73.6%, and the protection rates of the facial and trigeminal nerves was found as 100%. No statistically significant difference was detected in the distribution of the age, treatment dose, and tumor sizes in patients in accordance with the deterioration of hearing after treatment. Conformity index (CI), and coverage were found as the predictive factors in the protection of hearing.

Conclusion: The investigation of the stereotactic results of VSs in the literature showed that local control and hearing functions were moderately protected, and cranial nerve associated toxicity was found in moderate levels. The treatment parameters of CI and coverage were found as the predictive values in the protection of functional hearing after treatment. Randomized controlled prospective studies in patient groups with longer follow-up periods were required for ultimately determining the reliability of this treatment modality.

Keywords: Vestibular schwannoma, CyberKnife®, radiosurgery, radiotherapy, stereotaxy

ÖZ

Amaç: Serebellopontin köşenin en sık tümörü olan vestibüler schwannom (VS), benign nitelikte tümörler olmasına ve lokalizasyonları nedeniyle nadiren fatal seyretse de, semptomları hayat kalitesini bozar. Bu çalışmada VS'li hastaların tedavisinde uygulanan özellikle son dönemde intrakraniyal tümörlerde oldukça popüler non-invaziv ve keskin doz düşüşleriyle çevre dokulara minimum toksisite oluşturan CyberKnife® cihazı ile yapılan radyoterapi tedavisinin lokal tümör kontrolü, işitme fonksiyonları ve tedavinin yan etkileri açısından değerlendirilmesi amaçlanmaktadır.

Yöntemler: Bu çalışmada 28 VS tanılı hastaya CyberKnife® ile radyocerrahi veya stereotaktik radyoterapi uygulanmıştır. Bu olgular rutin radyolojik görüntüleme, odyolojik testler ve nörolojik fonksiyonların değerlendirilmesi ile takip edilmişlerdir. Çalışma retrospektif olarak yapılmış olup, hastalara ait veriler klinik takip arşiv dosyalarından elde edilmiştir.

Bulgular: VS tanılı 28 hastaya CyberKnife® ile stereotaktik radyoterapi uygulanmıştır. Hastaların ortalama takip süresi 40,25 aydır. Takiplerde lokal kontrol oranı %100, yeterli düzeyde işitmesi bulunan hastalarda işitmenin korunma oranı %73,6 ve fasiyal ile trigeminal sinirlerin korunma oranı %100 olarak

ORCID IDs of the authors: T.B. 0000-0002-4087-4760; S.G. 0000-0001-8585-9524; F.A. 0000-0002-0107-0735; S.Ç.K. 0000-0001-7947-8338



Corresponding Author/Sorumlu Yazar: Tanju Berber,

E-posta: tanjuberber@hotmail.com

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bulunmuştur. Tedavi sonrası işitmede bozulma olması durumuna göre olguların yaş, tedavi dozu, tümör boylarının dağılımları arasında istatistiksel olarak anlamlı farklılık saptanmamıştır. Konformite indeksi (Kİ) ve coverage ise işitmenin korunmasında prediktif faktörler olarak saptanmıştır.

Sonuç: Literatürdeki VS'lerin stereotaktik radyoterapi sonuçları incelendiğinde, hastalarda lokal kontrol ve işitme fonksiyonlarının makul ölçüde korunduğu ve kranial sinirlere bağlı toksisitenin kabul edilebilir seviyelerde olduğu görülmektedir. Tedavi parametrelerinden Kİ ve coverage tedavi sonrası işlevsel işitmenin korunması için prediktif değerler olarak bulunmuştur. Bu tedavi modalitesinin güvenilirliğini nihai olarak belirleyebilmek için takip süresi daha uzun olan hasta gruplarında randomize kontrollü prospektif çalışmalara ihtiyaç olduğu görülmektedir.

Anahtar kelimeler: Vestibüler schwannom, CyberKnife®, radyocerrahi, radyoterapi, sterotaksi

INTRODUCTION

The aim was to evaluate the tumor local control rates, hearing functions, and adverse effects of treatment in patients with clinically or radiologically proven cerebellopontin angle (CPA) tumor [vestibular schwannoma (VS) or meningioma], who were treated using the stereotactic radiosurgery (SRS) or fractionated radiosurgery (FSRT) method in Radiation Oncology CyberKnife® unit in Okmeydanı Training and Research Hospital between July 2012 and October 2014. Patients with tumor size higher than 3 cm or patients who had a history of previous surgical treatment were excluded from the study.

Approximately 10% of all intracranial tumors stemmed from the CPA, and VSs constituted the majority of the tumors of this region (1,2). These tumors, previously known as VS, constituted 6-8% of the primary intracranial brain tumors and 60-78% of the CPA tumors. Although benign, the results may be vexing. The prevalence rate was 1 in 100.000.

Approximately 2 mm/year growth of tumor in the internal auditory canal was evaluated as "gradual growth", and the growth higher than 10 mm/year was evaluated as "the rapid growth" of the tumor. 43% of the cases were in tendency of growth, 51% were stable, and 6% became smaller without any treatment in a collection of 21 literature studies consisting of 1345 patients who were followed up due to VS and the longer follow-up period was 3.2 years (3).

Radiosurgery treatment technique enables a noninvasive treatment option with similar local control rates, and with better protection of hearing and the better protection of the 5th and 7th cranial nerves compared to the surgical treatment (4), and the damage is reduced (5). Therefore, Cyberknife®, a non-invasive radiotherapy technique with sharp dose decreases has recently become popular in VS, and in other benign cranial pathologies compared to surgical treatment particularly with gamma knife. The recent data showed that higher local control and lower adverse effects could be obtained with 12-13 Gy dose in VS (6-9).

METHODS

Ethics committee approval was received for this study from the Ethics Committee of Okmeydanı Training and Research Hospital (approval number: 267, date: 03.02.2015). This is a retrospective study. Patient data were taken from the files.

Patients from all ages and sex, who were diagnosed with clinically and radiologically proven CPA tumor and who underwent CyberKnife® treatment in Okmeydanı Training and Research Hospital between 2012 and 2014 constituted the sampling of the

study. Patients with CPA tumor, who were recommended follow-up or who underwent surgery in Okmeydanı Training and Research Hospital between 2012 and 2014, were excluded from the study. All patients included in the study were diagnosed with VS, and the diagnosis was put in a council consisting of the physicians of radiation oncology, radiology, otorhinolaryngology, neurosurgery, and pathology. The decision of stereotactic radiation treatment was taken after discussion with patients who were thought to be suitable for CyberKnife® treatment in tumor council. A total of 28 patients consisting of 17 women and 11 men were included. Physical and neurologic examinations were performed before the treatment. Hearing tests and 5th and 7th cranial nerve examinations using the Gardner-Robertson hearing scale were performed before the treatment in patients diagnosed with VS.

Different fraction schemas were selected as the treatment dose in accordance with the tumor diameter, volume, and the proximity to the neighboring tissue in the present study. 3 (10.7%) patients received radiosurgery under 1x12 Gy irradiation and 11 (39.2%) received 3x6 Gy (18 Gy), 2 (7.1 %) patients received 3x7.5 (22.5 Gy), 1 (3.5%) patient received 3x8 Gy (24 Gy), and 11 (39.2%) patients received 5x5 Gy (25 Gy) radiation treatment. 1x12 Gy radiosurgery was administered for 3 patients who had a tumor diameter smaller than 1 cm, and a total of 18-25 Gy radiation was administered in 3 to 5 fractions for the tumors larger in diameter than 1 cm (10-12).

The hearing functions of all patients before and after CyberKnife® treatment were evaluated using audiometry. Pure tone threshold audiogram, the average pure tone, speech recognition threshold, and Speech Discrimination score were investigated in pure tone audiometry. Gardner-Robertson class for each patient was identified using the pure tone average, and speech discrimination scores (13). The patient group in class 1 was able to speak on the phone with the affected side. The patient group in class 2 (with pure tone audiogram threshold lower than 50 dB, and speech discrimination score higher than 50%) was accepted in the critical threshold for hearing. The hearing levels of patients in class 1 and 2 were evaluated as moderate levels. The hearing levels of patients in class 3 and in poor levels were evaluated as inadequate and/or poor.

Diagnosis of all patients were performed using the radiologic screening. Magnetic resonance imaging (MRI) and computed tomography (CT) were used in radiologic screening. CT and contrast enhanced MRI screening of all patients were performed before the treatment, and tumor size and tumor localization were identified. Post-treatment local tumor control follow-up was performed using the contrast enhanced MRI. The tumor was

contoured in each axial section over these images, and tumor diameter and tumor volume were measured.

The 5th, 7th, and 8th nerves were clinically evaluated before and after the treatment. The House & Brackmann classification was used in the clinical evaluation of the facial nerve function. Trigeminal nerve functions were evaluated as the normal, increased, or decreased sense using a semiquantitative scale. The functions of the other cranial nerves were recorded as temporary and permanent deficit.

The symptoms of all patients before and after the treatment (headache, tinnitus, ataxia, vertigo, etc.) were questioned and recorded to the clinical files. Scoring of headache could not be performed; however, the presence or absence of headache was evaluated. The symptoms were recorded as maintained, disappeared in the routine follow-ups.

Statistical Analysis

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used in the statistical analysis of the data. The compliance of parameters to normal distribution was evaluated using the Shapiro-Wilks test. Student's t-test was used in the comparison of parameters in normal distribution, and The Mann-Whitney U test was used in the comparison of non-normal distribution between two groups in the quantitative comparison of data, in addition to the descriptive statistical methods (mean, standard deviation, and frequency) in the evaluation of the study data. The paired sample t-test was used in the pretreatment-posttreatment comparisons of the normal distribution parameters, and the Wilcoxon signed test was used in the comparisons of the non-normal distribution parameters. The McNemar test was used in the comparison of the qualitative data. Pearson's correlation analysis was used in investigating the association between the parameters in normal distribution, and the Spearman's rho correlation analysis was used in the investigation of the association of parameters in non-normal distribution. The significance was evaluated in $p < 0.05$ level.

RESULTS

The present study was performed with 28 patients diagnosed with VS, who were administered Cyberknife® stereotactic radiotherapy between July 2012 and October 2014.

The patient characteristics, tumor, and treatment parameters are summarized in Table 1. The comparison of the pretreatment tumor diameter and volume and hearing tests with post-treatment values were not statistically significantly different between the mean tumor diameter before the treatment and after the treatment ($p > 0.05$). There was no statistically significant difference between the tumor volumes before the treatment and after the treatment ($p > 0.05$). No statistically significant difference was detected in tumor diameter and volume in the mean 40.25 ± 7.68 (30-54 months) months follow-up after the treatment, and the local control rate was 100%.

The increase in the mean sensorineural audiogram (SSA) score after the treatment was found to be statistically significant compared

to the score before the treatment ($p = 0.001$; $p < 0.01$, respectively). The decrease in the mean speech discrimination score after the treatment was found to be statistically significant compared to the value before the treatment ($p = 0.024$; $p < 0.05$, respectively). No statistically significant difference was detected in Gardner-Robertson scores before and after the treatment ($p > 0.05$).

There was a statistically significant association to negative direction between the CI and the change differences in SSA scores before and after the treatment in 57.3% levels ($r = -0.573$; $p = 0.001$; $p < 0.01$). There was a statistically significant association in positive direction between the coverage values and the change differences of SSA scores before and after the treatment in 59.6% levels ($r = 0.596$; $p = 0.001$; $p < 0.01$).

The correlation of the change in speech discrimination in accordance with the tumor size and treatment parameters was statistically significantly associated with positive direction between the CI values and the change differences in the speech discrimination scores before and after the treatment in 38% levels ($r = 0.380$; $p = 0.046$; $p < 0.05$).

Table 1. Patient, tumor, and treatment characteristics

	Minimum-maximum	Mean \pm SD
Age (year)	26-71	50.14 \pm 12.71
Sex (n%)		
Woman	17	60.7
Man	11	39.3
Age groups (n%)		
Below 60 years	23	82.1
60 years and above	5	17.9
Follow-up time (month)	30-54	40.25 \pm 7.68
Pre-treatment tumor diameter (mm)	11-29	17.89 \pm 5.65
Post-treatment tumor diameter (mm)	10-28	17.61 \pm 5.45
Pre-treatment tumor volume	360-12600	3206.93 \pm 3500.68
Post-treatment tumor volume	359-12591	3203.75 \pm 3496.02
Pre-treatment SSA score	0-92	40.46 \pm 26.58
Post-treatment SSA score	8-92	48.89 \pm 25.81
Pre-treatment speech discrimination score	4-100	59.07 \pm 31.29
Post-treatment speech discrimination score	6-94	54.21 \pm 28.06
Pre-treatment GR score	1-5	2.04 \pm 1.07
Post-treatment GR score	1-5	2.18 \pm 1.19
CI	1.18-1.85	1.32 \pm 0.14
HI	1.13-1.55	1.25 \pm 0.08
Coverage	95.2-99.9	98.35 \pm 1.16
Mean cochlear dose	98-2305	1177.04 \pm 594.42
SD: standard deviation, SSA: sensorineural audiogram, GR: Gardner-Robertson, CI: Conformity index, HI: Homogeneity index		

The effects of age and sex on the speech discrimination were demonstrated in Table 2.

The rate of the protection of hearing was found as 73.6% in the study. Deterioration was detected in hearing functions of 5 patients who had pretreatment functional hearing.

No toxicity associated with facial, trigeminal, and other cranial nerves was detected before and after the treatment. The protection rate of the facial and trigeminal nerve functions was found as 100% in the present study.

No pseudoprogession was detected in the routine radiological follow-up of the patients in the study.

The decrease in the rate of ataxia after the treatment (3.6%) was found to be statistically significant compared to the rate of ataxia before the treatment (25%) ($p=0.031$; $p<0.05$). The decrease in the detection rate of headache after the treatment (32.1%) was found to be statistically significant compared to the detection rate of headache (60.7%) before the treatment ($p=0.021$; $p<0.05$).

DISCUSSION

VSs constitute 6-8% of primary intracranial brain tumors and 60-78% of CPA tumors (13). The prevalence is 1 in 100.000 (14). In parallel with the developments in radiologic screening, the diagnosis of VS may be accomplished when the tumor size is smaller. The studies which evaluated the treatment in VS were retrospective, and the evidence level of the studies were level 3 or smaller (15). Therefore, there is a lack of evidence-based guide in treatment. The increase of the treatment options in VS and the scarce number of randomized and controlled studies of treatment options led the physicians to interdisciplinary study, and to evaluation in the diagnosis and treatment of the disease. VS is rarely life-threatening, thus the main target in treatment is to provide local tumor control and to protect the moderate hearing and organ functions. The tumor size, age, the general condition of the patient, whether the hearing will be protected, the chance of the protection of the 5th and 7th nerves, tumor growth rate, the presence of neurofibromatosis type 2, the adequate local tumor control, and the treatment associated adverse events are considered in the selection of the treatment. The current treatment approaches are close follow-up, SRS, fractioned radiotherapy, and microsurgery resection. The aim in the CyberKnife® radiosurgery

and FSRT treatment techniques is to pause the tumor growth or to minimize the tumor by administrating radiation in a single or several sessions. CyberKnife® functions in the guidance of the real time screening, and rigid immobilization of patient is not required. The comparison of the treatment results of CyberKnife® radiosurgery (steerotactic radiosurgery) and FSRT with surgical treatment showed that similar local control rates were obtained. In addition, this method provides a noninvasive treatment option with the possibility of the better protection of the 5th and 7th cranial nerves (16).

Three patients were administered CyberKnife® radiosurgery at 12 Gy, and 25 patients were administered FSRT between 18 and 25 Gy in the present study. Local control rate was found as 100%. The treatment doses and local control rates in our study were parallel with the doses and local control rates of the other researchers; however, the mean follow-up period was between 5 and 10 years in the studies in the literature, and our mean follow-up time was 40 (40.25±7.68 months) months. Therefore, the possible progressions in our longer period follow-ups may cause lower local control rates.

Pseudoprogession is generally detected in the first 2 years after radiosurgery. Hathout showed that the pseudoprogession rate was higher in patients who underwent previous surgery before SRS (17). Therefore, treatment should not be regarded unsuccessful before the month 24 of the treatment, and treatment approach should not be changed before the month 36 unless there is a clinical requirement (18). We detected no pseudoprogession in the patients in our study group, which may be explained by that the patients who underwent previous surgery were excluded from the study.

The use of fractioned stereotactic radiotherapy for VSs minimizes the radiation associated damage of the neighboring cranial nerves compared to the use of single fraction radiosurgery. The facial and trigeminal toxicity rate was found as 5% in the 4- year follow-up of 37 patients who were administered CyberKnife® FSRT (10-12). The facial nerve protection rate was reported as 74-100%, and the trigeminal nerve protection rate was reported as 73-100% in an analysis which evaluated 17 studies in the literature (19). We detected no toxicity associated with facial and trigeminal nerves in patients who were administered SRS or FSRT in our study. The protection rate of cranial nerves was 100%, which was similar with the results in the literature.

A summary of the other studies in the literature and of our study is presented in Table 3 (7,20-23). As Cyberknife® is a relatively new device in our country, there are not enough studies on this subject yet.

Our study was similar to the studies in the literature regarding the local control, moderate hearing, and cranial nerves protection rates (20,24-26). There were differences in the studies investigating the predictive factors demonstrating the moderate hearing level after the treatment. No significant association of factors such as age, sex, tumor size, tumor volume, mean cochlear dose, and

Table 2. The effects of age, and sex on the speech discrimination

		Pretreatment-post treatment speech discrimination score	p
		Mean ± SD (median)	
Sex	Woman	-1.06±22.84 (-3)	0.220
	Man	-10.73±14.13 (-7)	
Age groups	Below 60 years	-4.83±22.15 (-3)	0.928
	Sixty years and above	-5±6.67 (-3)	

Mann-Whitney U test, SD: standard deviation

Table 3. A summary of the other studies in the literature and of our study

Author	No of patients	Dose (Gy)	Fraction	Local control rate (%)	Hearing protection rate (%)	Facial nerve protection rate (%)	Trigeminal nerve protection rate (%)	Follow-up (month)
Murphy and Suh (14)	117	13	1	91	Unknown	95	99	38
Chopra et al. (24)	216	13	1	92	44	100	95	68
Noren (13)	669	Unknown	1	95	65-70	Unknown	Unknown	Unknown
Kondziolka et al. (12)	162	16	1	98	51	79	73	60-120
Iwai et al. (30)	25	12	1	96	64	96	100	89
Szumacher et al. (31)	39	50	25	95	68	95	95	22
Maire et al. (32)	45	50.4	28	86	78	100	100	80
Fuss et al. (33)	51	57.6	32	98	85	100	96	42
Shirato et al. (34) ²	65	50	25	92	Unknown	Unknown	Unknown	37
Henze et al. (35)	39	54	Unknown	95	Unknown	Unknown	Unknown	36
Kapoor et al. (36)	385	25	5	97	Unknown	98	97	52
Meijer et al. (25)	80	25	5	94	61	97	98	33
Sakanaka et al. (37)	12	20	5	92	80	100	100	40
Williams al. (38)	125	25	5	100	Unknown	100	98	22
Chang et al. (16)	61	18	3	98	74	100	97	48
Poen et al. (39)	31	21	3	97	77	97	84	24
Ishihara et al. (40)	28	17	3	94	93	100	100	32
Our study	28	12-25	1-5	100	73.6	100	100	40

Homogeneity index was found with the hearing protection in our study (27-29). The moderate CI and coverage rates in treatment were found as the predictive values for hearing protection.

CONCLUSION

The investigation of the stereotactic radiotherapy results of VSs showed that local control was obtained, hearing functions were protected in moderate levels, and cranial nerve-associated toxicity was in moderate levels. CyberKnife® stereotactic radiotherapy is a good treatment option in VS patients particularly with tumor diameter smaller than 3 cm. Randomized controlled prospective studies in patient groups with longer follow-up period are required for the ultimate identification of the reliability of this treatment modality and for preparing a guideline.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Okmeydanı Training and Research Hospital (approval number: 267, date: 03.02.2015).

Informed Consent: This is a retrospective study. Patient data were taken from the files.

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Hasta Onamı: Bu retrospektif bir çalışmadır. Hasta verileri dosyalardan alınmıştır.

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