DOI: 10.5152/jarem.2018.2536

Manuscript Type: Original Article

Turkish Title: Vestibuler Schwanomalarda Cyberknife ile Stereotaktik Radyoterapi Uygulanan Hastalarda Lokal Tümör Kontrolünün ve Tedavinin Yan Etkilerinin Retrospektif Olarak Değerlendirilmesi
Turkish Running Head: Vestibuler Schwanomalarda Stereotaksi

Title: Results of Vestibular Schwannomas Treated By Cyberknife® and Stereotactic Radiotherapy: A Retrospective Study

Running Head: Stereotaxi of Vestibular Schwanomas

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Cite this article as: Berber T, Günenç S. Results of Vestibular Schwannomas Treated By Cyberknife® and Stereotactic Radiotherapy: A Retrospective Study. JAREM 2018; DOI: 10.5152/jarem.2018.2536

Received: 02.10.2018

Accepted: 05.12.2018

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ABSTRACT

Objective: Although the most common tumor of the cerebellopontin angle of the vestibular schwannomas are benign tumors and are rarely fatal due to their localisations, 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 recent popular noninvasive procedure causing minimum toxicity in the neighboring tissues with sharp dose decreases in treatment of patients with vestibular schwannoma particularly in intracranial tumors.

Methods: Cyberknife® radiosurgery were administered to 28 patients diagnosed with vestibular schwannoma 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 retrospectivelly, and the data of the patients were obtained from the archive files.

Results: CyberKnife® stereotactic radiotherapy was administered to 28 patients diagnosed with vestibular schwannoma. 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 wasfound 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, and coverage were found as the predictive factors in the protection of hearing.

Conclusion: The investigation of the stereotactic results of vestibular schwannomas 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 conformity index(CI), and coverage were found as the predictive values in the protection of functional hearing after treatment. Randomised 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

ÖZET

Amaç: Serebellopontin köşenin en sık tümörü olan vestibüler schwannom, benign nitelikte tümörler olmasına rağmen lokalizasyonları nedeniyle nadiren fatal seyretse de,semptomları hayat kalitesini bozar. Bu çalışmada vestibuler schwannomlu hastaların tedavisinde uygulanan özellikle son dönemde intrakranial tümörlerde oldukça popüler non invaziv ve keskin doz düşüşleriyle çevre dokulara minumum toksisite oluşturan CyberKnife® cihazı ile

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yapılan radyoterapi tedavisinin lokal tümör kontrolü, işitme fonksiyonları ve tedavinin yan etkileri açısından değerlendirilmesi amaçlanmaktadır.

Yöntemler: Bu çalışmada 28 vestibüler schwannom tanılı hastaya CyberKnife® ile radyocerrahi veya sterotaktik 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: Vestibuler schwannom tanılı 28 hastaya CyberKnife® ile sterotaktik radyoterapi uygulanmıştır. Hastaların ortalama takip süres 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 bulunmuştur. Tedavi sonrası işitmede bozulma olması durumuna göre olguların yaş, tedavi dozu, tümör boylarının dağılımları arasında istatistiksel olarak anlamlı farklılık saptanmamıştır. Konformite indeksi (CI) ve coverage'ın ise işitmenin korunmasında prediktif faktörler olarak saptanmıştır.

Sonuç: Literatürdeki Vestibüler Schwannomların stereotaktik radyoterapi sonuçları incelendiğinde, hastalarda lokal kontrol, işitme fonksiyonlarının makul ölçüde korunduğu ve kranyal sinirlere bağlı toksisitenin kabul edilebilir seviyelerde olduğu görülmektedir. Tedavi parametrelerinden CI ve coverage'ın 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 tumor (vestibular schwannoma or meningioma) who were treated using the SRS (stereotactic radiosurgery) or FSRT (franctionated radiosurgery) method in Radiation Oncology CyberKnife® unit in XXXXXX 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 cerebellopontin angle (CPA), and vestibular schwannomas constituted the majority of the tumors of this region(1

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2) These tumors previously known as vestibular schwannoma, constituted 6-8% of the primary intracranial brain tumors, and 60-78% of the cerebellopontin angle 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 is evaluated as 'gradual growth', and the growth higher than 10mm/year is 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 (vestibular schwannom) 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 with the surgical treatment(4), and the damage is reduced(5). Therefore, Cyberknife®, a noninvasive radiotherapy technique with sharp dose decreases has recently become popular in VS, and in other benign cranial pathologies compared with 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 vestibular schwannoma(6 7 8 9).

Methods

Patients from all ages, and sex diagnosed with clinically and radiologically proven CPA tumor, and who underwent CyberKnife® treatment in xxxxx 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 xxxxxx 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, and neurosurgery, and pathology. The decision of stereotactic radiation treatment was taken after discussion of 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 treatment. Hearing tests, and 5th and 7th cranial nerve examinations using the Gardner-Robertson hearing scale were performed before treatment in patients diagnosed with vestibular schwannoma.

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

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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 11 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 were able to speak on the phone with the affected side. The patient group in Class 2 (with pure tone audiogram threshold lower than 50dB, and speech discrimination score higher than 50%) is accepted in the critical threshold for hearing. The hearing levels of patients in Class 1, and 2 were evaluated as in 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. Computed tomograpy and contrast enhanced MRI screening of all patients were performed before treatment, and tumor size, and tumor localisation 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 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 treatment (headache, tinnitus, ataxia, vertigo, etc.) were questioned, and recorded to the clinical files. Scoring of headache could not be performed however, presence or absence of headache was evaluated. The symptoms were recorded as maintained, disappeared in the routine follow-ups.

Ethics committee approval was obtained from the local ethic committee.

Statistical Analysis

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The IBM Statistical Package for the Social Sciences (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 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 disribution 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 Wilcoxon signed test was used in the comparisons of the non-normal distribution parameters. Mc Nemar 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 vestibular schwannoma who were administered Cyberknife® stereotactic radiotherapy between July 2012, and October 2014.

The patient characteristics, tumor, and treatment parameters are summarised in the table 1. The comparison of the pretreatment tumor diameter and volume, and hearing tests with post-treatment values were no statistically significant difference between the mean tumor diameter before treatment, and after treatment ($p>0.05$). There was no statistically significant difference between the tumor volumes before treatment, and after 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 treatment, and the local control rate was 100%.

The increase in the mean sensorineural audiogram (SSA) score after treatment was found statistically significant compared with the score before treatment (p:0.001; $p<0.01$, respectively). The decrease in the mean speech discrimination score after treatment was found statistically significant compared with the value before treatment (p:0.024; $p<0.05$,respectively). No statistically significant difference was detected in GR scores before, and after 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 treatment in 57.3% levels (r:-0.573; p:0.001; $p<0.01$). There was a statistically significant association in positive direction

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between the coverage values and the change differences of SSA scores before and after 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 were statistically significant association in positive direction between the CI values, and the change differences in the speech discrimination scores before and after treatment, in 38% levels (r:0.380; p:0.046; p<0.05).

The effects of age, and sex on the speech discrimination were demonstrated in the 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 treatment. The protection rate of the facial, and trigeminal nerve functions was found as 100% in the present study.
No pseudoprogression was detected in the routine radiological follow-up of the patients in the study.
The decrease in the rate of ataxia after treatment (3.6%) was found statistically significant compared with the rate of ataxia before treatment (25%) (p:0.031; p<0.05). The decrease in the detection rate of headache after treatment (32.1%) was found statistically significant compared with the detection rate of headache (60.7%) before treatment (p:0.021; p<0.05).

Discussion

Vestibular schwannomas constitute the 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 randomised and controlled studies of treatment options led the physicians to interdisciplinary study, and to evaluation in the diagnosis and treatment of the disease. Vestibular schwannoma 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 NF (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, stereotactic radiosurgery, fractioned radiotherapy, and microsurgery resection. The aim in the CyberKnife® radiosurgery, and FSRT treatment technique is to pause the tumor growth or

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to minimise the tumor by administrating radiation in a single or several sessions. CyberKnife® functions in the guidance of the real time screening, and rigid immobilisation of patient is not required. The comparison of the treatment results of CyberKnife® radiosurgery (steorotactic radiosurgery), and FSRT (fractioned sterotactic radiation therapy) 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).

3 patients were administered CyberKnife® radiosurgery at 12 Gy, and 25 patients were administered FSRT between 18-25 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- 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.

Pseudoprogression is generally detected in the first 2 years after radiosurgery. Hathout showed that the pseudoprogression 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 month 36 unless there was a clinical requirement(18). We detected no pseudoprogression in the patients in our study group which may be explained that the patients who underwent previous surgery were excluded from the study.

The use of fractioned stereotactic radiotherapy for vestibular schwannomas minimises the radiation associated damage of the neighboring cranial nerves compared with the use of single fraction radiosurgery. The facial, and trigeminal toxicity rate was found as 5% in the 4 years follow-up of 37 patients who were administered CyberKnife® FSRT(10 11 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 the below table 3(7 20 21 22 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 25 26). There were differences in the

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studies investigating the predictive factors demonstrating the moderate hearing level after treatment. No significant association of factors such as age, sex, tumor size, tumor volume, mean cochlear dose, and homogenity index was found with the hearing protection in our study(27 28 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 vestibular schwannomas showed that local control was obtained, hearing functions were protected in moderate levels, and cranial nerve-associated toxicity was in moderate levels. CyberKnife® stereotacticradiotherapy is a good treatment option in VS patients particularly with tumor diameter smaller than 3 cm. Randomised 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.

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Table 1: Patient, tumor, and treatment characteristics

		Min-Max	Mean±SD
Age (year)		26-71	50.14±12.71
Sex$_{n, \%}$			
Woman		17	60.7
	Man	11	39.3
Age groups$_{n, \%}$			
Below 60 years		23	82.1

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60 years and above	5	17.9
Follow-uptime (month)	30-54	40.25±7.68
Pretreatmenttumor diameter (mm)	11-29	17.89±5.65
Post treatment tumor diameter (mm)	10-28	17.61±5.45
Pretreatment tumor volume	360-12600	3206.93±3500.68
Post treatment tumor volume	359-12591	3203.75±3496.02
Pretreatment SSAscore	0-92	40.46±26.58
Post treatment SSAscore	8-92	48.89±25.81
Pretreatment speech discrimination score	4-100	59.07±31.29
Post treatment speechdiscriminationscore	6-94	54.21±28.06
Pretreatment GR score	1-5	2.04±1.07
Post treatment GR score	1-5	2.18±1.19
CI	1.18-1.85	1.32±0.14
HI	1.13-1.55	1.25±0.08
Coverage	95.2-99.9	98.35±1.16
Mean cochlear dose	98-2305	1177.04±594.42

SSA(Sensorineural audiogram)

GR(Gardner-Robertson) CI(conformity index),HI(homogenity index)*

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

		Pretreatment - Post treatment Speech Discrimination Score Mean±SD(Median)	**p**
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**
	60 years and above	-5±6.67 (-3)	

Mann-Whitney U Test

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 et al.	117	13	1	91	Unknown	95	99	38
Chopra et al.	216	13	1	92	44	100	95	68
Noren et al.	669	Unknown	1	95	65-70	Unknown	Unknown	Unknown
Kondziolka et al.	162	16	1	98	51	79	73	60-120
Iwai et al.	25	12	1	96	64	96	100	89
Szumacher et al.	39	50	25	95	68	95	95	22
Maire et al.	45	50.4	28	86	78	100	100	80
Fuss et al.	51	57.6	32	98	85	100	96	42
Shirato et al.	65	50	25	92	Unknown	Unknown	Unknown	37
Henze et al.	39	54	Unknown	95	Unknown	Unknown	Unknown	36
Kapoor et al.	385	25	5	97	Unknown	98	97	52

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Meijer et al.	80	25	5	94	61	97	98	33
Sakanaka et al.	12	20	5	92	80	100	100	40
Williamset al.	125	25	5	100	Unknown	100	98	22
Chang et al.	61	18	3	98	74	100	97	48
Poen et al.	31	21	3	97	77	97	84	24
Ishihara et al.	28	17	3	94	93	100	100	32
Our study	28	12-25	1-5	100	73.6	100	100	40

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