

Clinical, radiological and toxicity evaluation of Vestibular Schwannoma patients treated with Cyberknife® stereotactic radiosurgery-radiotherapy

CyberKnife stereotaktik radyocerrahi- radyoterapi ile tedavi edilen Vestibuler Schwannoma hastalarının klinik, radyolojik ve toksisite açısından değerlendirilmesi

Gonca Altınışık İnan¹, Süheyla Aytaç Arslan², Ebru Karakaya³, Yıldız Güney⁴

¹Ankara Atatürk Eğitim Ve Araştırma Hastanesi, Radyasyon Onkolojisi Kliniği, Ankara

²Yıldırım Beyazıt Üniversitesi Tıp Fakültesi, Radyasyon Onkolojisi Bölümü

³Ankara Abdurrahman Yurtaslan Onkoloji Eğitim Ve Araştırma Hastanesi, Radyasyon Onkolojisi Kliniği

⁴Memorial Ankara Hastanesi, Radyasyon Onkolojisi Kliniği

Dergiye Ulaşma Tarihi:28.05.2018 Dergiye Kabul Tarihi:05.11.2018 Doi: 10.5505/aot.2019.88700

ÖZET

GİRİŞ ve AMAÇ: Bu çalışmada amaç CyberKnife stereotaktik radyocerrahi-radyoterapi uygulanan vestibuler schwannom hastalarının klinik, radyolojik ve toksisite verilerinin sunulmasıdır.

YÖNTEM ve GEREÇLER: Çalışma, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi Kliniği'nde Haziran 2009 - Eylül 2014 tarihleri arasında vestibuler schwannom tanısı ile CyberKnife® (Accuray, Sunnyvale) cihazında stereotaktik radyocerrahi ve stereotaktik radyoterapi uygulanan hastaların klinik ve radyolojik değerlendirmeleri bununla birlikte tedavi öncesi ve son kontrollerine ait işitme değerlendirmesi (Gardner-Robertson skalası), 7. kranial sinir motor fonksiyon değerlendirmesi (House-Brackmann skalası), 5. kranial sinir duyu muayenesi sonuçları ile toksisite değerlendirmesi yapılmıştır.

BULGULAR: Lokal kontrol, radyolojik stabil veya regresif hastalık olarak tanımlandı ve tüm hastaların son kontrollerinde %100 olarak saptandı. GRS ve HB skoru tedavi öncesi değerleri tedavi sonrası değerlerinden istatistiksel olarak anlamlı farklı bulunmuştur (p= 0,042 ve p= 0,046).Trigeminal toksisite %7 oranında saptanmıştır.

TARTIŞMA ve SONUÇ: Çalışmada lokal kontrol oranları literatür ile benzerlik göstermekle birlikte trigeminal toksisite oranı yüksek bulunmuştur. Doz ve fraksiyon şemalarının optimizasyonu için prospektif çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Vestibuler schwannoma, Stereotaktik radyoterapi, Stereotaktik radyocerrahi, CyberKnife

ABSTRACT

INTRODUCTION: The current study was done by means of clinical and radiological evaluations of vestibular schwannoma patients who treated with stereotactic radiosurgery or stereotactic radiotherapy using Cyberknife® (Accuray, Sunnywhale, USA).

MATERIAL and METHODS: Between June 2009 and September 2014,30 vestibular schwannoma patients were treated in Dr. AY. Ankara Oncology Training and Research Hospital, Department of Radiation Oncology. The patients were assessed before and after radiotherapy retrospectively, for hearing capacity (via Gardner-RobertsonScale), motor function of cranial nerve 7. (via House-Brackmannscale),the sensorial function of cranial nerve 5.

RESULTS: Local control was defined as radiologically stable or regressive disease and achieved for all of the patients at the last control (%100). Preradiotherapy mean values of GRS and HB scores were both statistically different from post radiotherapy mean values (p=0,042 and p=0,046, respectively). Trigeminal toxicity was determined as 7%.

DISCUSSION AND CONCLUSION: When the study results were interpreted, while the local control results were found similar with the literature, trigeminal nerve toxicity values were higher than the reported results. Prospective studies are needed to optimize dose and fraction schedules.

Keywords: Vestibular schwannoma, Stereotactic radiosurgery, Stereotactic radiotherapy, Cyberknife.

INTRODUCTION

Vestibular schwannomas (VS) are benign tumours of Schwann cell origin that occur on the eighth cranial nerve. They are known also

as acoustic neuromas and account for approximately 8% of all tumors inside the skull¹. In recent years, an increasing incidence of diagnosed vestibular schwannoma has been reported by several centers². The most common symptom is unilateral hearing loss by the tumor effect through either direct progressive injury to the cochlear nerve (slowly progressive sensorineural hearing loss) or interruption of cochlear blood supply (sudden and fluctuating hearing losses)³. Other commonly presenting symptoms are tinnitus and balance disturbance, with its tumor progression can lead to brainstem compression, cranial neuropathies and hydrocephalus⁴. To manage the VS include 4 strategies: observation, microsurgical resection, stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (SRT)^{4,5}. Tumor size, age, severity and duration of symptoms, the patient preference and the clinician experience are the factors for determining which option should be undertaken for a particular case. There is no international consensus regarding the optimal treatment for vestibular schwannoma⁶.

Stereotactic radiation therapy is a type of external beam radiation therapy and can be delivered in two ways: 1. Stereotactic radiosurgery (SRS) delivers a single high dose of radiation to the tumour 2. Stereotactic radiotherapy (SRT) gives relatively smaller doses of radiation over a number of treatment sessions (called multiple, ex 1-5 fractions). Stereotactic radiosurgery was administered for vestibular schwannoma treatment using the Gamma Knife[®] by Leksell in 1969⁷, henceforth stereotactic radiotherapy is increasingly used in the management of patients with vestibular schwannomas⁶. While many papers and review articles report satisfactory tumour growth control and few side effects with stereotactic radiosurgery/radiotherapy there is no consensus about which patient suitable for this treatment and RT parameters such as prescription dose, number of fractions etc. In this study we aimed to assess tumour control, hearing preservation status and complication rate after fractionated SRS/SRT by using CyberKnife[®] in patients with VS and to contribute the literature with the study results.

PATIENTS and METHODS

Address for correspondence: Uzm. Dr. Gonca Altınışık İnan, Ankara Atatürk Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi Kliniği Ankara - Türkiye
e-mail: goncaaltinisikin@gmail.com
Available at www.actaoncologica.turcica.com
Copyright ©Ankara Onkoloji Hastanesi

In the present study, we retrospectively reviewed 30 adult patients with 31 tumor sites, aged 18 years or older diagnosed as vestibular schwannoma treated with SRS at Ankara Oncology Hospital Radiation Oncology Clinic between June 2009 and September 2014. Data was obtained from patients' medical charts and RT documents. Patients were included only if they had radiologic and/or pathologic confirmation and had their follow-up at our institution. Clinical assessment was done using with preRT and postRT Gardner Robertson Score (Table 1) for hearing evaluation and House-Brackman scale (Table 2) to quantify facial function. Tumour was assessed using Koos classification (Table 3) which is a common classification system frequently used for vestibular schwannoma⁸. Trigeminal nerve toxicity was also evaluated. Patients clinically assessed based on the presence or absence of: hypoesthesia, anesthesia and hyperesthesia. Patients had pre RT Response evaluation to treatment was done using gadolinium enhanced MRI and aforementioned tests.

Radiation Therapy

All the patients were immobilized in a fixed position with custom-made thermoplastic masks and simulated at computed tomography (CT) with a 1.5 mm slice thickness. These CT images were fused with the magnetic resonance imaging (MRI) images of the same slice thickness. Gross total volumes (GTVs) were delineated using contrast enhancement on T1-weighted series and an extra 1-mm margin was added to form planning target volume (PTV) depending on the discretion of treating physician.

Brainstem, chiasma, bilateral cochleas, internal acoustic canals, hippocampuses, eyes, lenses, optic nerves and healthy brain tissue outside the GTV were contoured as organs at risk. The contoured images were then sent to Cyberknife planning system and a prescribed dose of 11,25-22,50 Gy in 1-5 fractions were planned using sequential technic and applied with 6D skull tracking (figure 1).

Statistics

The collected data were evaluated using Statistical Package for Social Sciences (SPSS) for Windows 11.5.

$p=0.05$ was considered statistically significant.

RESULTS

Total of 30 adults with 31 lesions treated at Ankara Oncology Hospital were reviewed. Patients demographics and clinical characteristics are presented in Table 4. The median follow up was 21 (range, 2-57) months. Median age at diagnosis was 47 years ranging from 25 to 77 and male to female ratio was 14 / 16 with a slightly female predominance. Prescribed dose was median 18 Gy (range, 10-22.5) with a median of 6 Gy (4-13) in median 3 (1-5) fractions. RT was delivered as a single fraction in 4 (13%) patients and every other day in the rest of 10 (37%). According to the Koos grading, the most predominant type was group 2 (n=18, 58%) and lesions were mostly right side located (n=19, 63%).

Gadolinium enhanced MRI revealed a 64.5% partial response and 35.5% stable disease so an overall 100% local control achieved during a median 20 months (range, 2-57) follow-up.

When the plan data were evaluated median coverage, homogeneity index (HI), conformity index (CI), new conformity index (nCI), and monitor unit (MU) values were %97,42 (92,97-99,90), %87 (71-95), 1,15 (1,05-1,41), 1,39 (1,1-2,33), 1,44 (1,13-2,33) ve 18405 (3276-36448) respectively.

Of the 30 patients, 11 (35%) had nonservicable hearing before treatment and one of them progressed to servicable hearing after treatment. Four of nineteen patients with servicable hearing worsened after RT (three patients had received 18 Gy / 3 fr and remaining one had received 12.5 Gy / 1 fr) to nonservicable hearing. PostRT decreases in GRS was statistically significant (p=0,042). But the difference between pre and post RT GRS was not associated with cochlear dosimetry (1cc, max and mean and central).

Facial nerve assesment was done using pre and post RT House Berckman scoring. All patients except one (grade 4) had grade 1 facial nerve function before treatment. Scores worsened in 4 of 29 patients after RT and no change was seen in patient previously graded 4, facial nerve toxicity rate was 13.3% and decrease in HB score was statistically significant (p=0.046).

Pre-treatment trigeminal assessment of the patients was done by grouping them as hypoesthesia, normal and hyperesthesia. Only one patient had sensory loss before treatment. The sensory loss in this case continued in the same way after the treatment. In addition, hypoesthesia was observed in 1 case, and hyperesthesia in 1 case was observed in 2 cases which pre-treatment trigeminal sensory function was normal. Based on these data, it was determined that the trigeminal toxicity ratio was 7%.

Table 1: Gardner –Robertson Score

	pure tone audiogram (dB)	speech discrimination (%)
Grade I (good-excellent)	0-30	70-100
Grade II (serviceable)	31-50	50-69
Grade III (non-serviceable)	51-90	5-49
Grade IV (poor)	91-max	1-4
Grade V (none)	not testable	0

Table 2: House-Brackmann facial nerve grading system

Grade I	Normal facial function in all areas
Grade II	Slight Dysfunction Gross: slight weakness noticeable on close inspection; may have very slight synkinesis At rest: normal symmetry and tone Motion: forehead - moderate to good function; eye - complete closure with minimum effort; mouth - slight asymmetry.
Grade III	Moderate Dysfunction Gross: obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, and/or hemi-facial spasm. At rest: normal symmetry and tone Motion: forehead - slight to moderate movement; eye - complete closure with effort; mouth - slightly weak with maximum effort
Grade IV	Moderate Severe Dysfunction Gross: obvious weakness and/or disfiguring asymmetry At rest: normal symmetry and tone Motion: forehead - none; eye - incomplete closure; mouth - asymmetric with maximum effort.
Grade V	Severe Dysfunction Gross: only barely perceptible motion At rest: asymmetry Motion: forehead - none; eye - incomplete closure; mouth - slight movement
Grade VI	Total Paralysis No movement

Table 3: Koos grading scale

Grade 1	Tumors involve only the internal auditory canal.
Grade 2	Tumors extend into the cerebellopontine angle, but do

	not encroach on the brainstem
Grade 3	Tumor fills the entire cerebellopontine angle.
Grade 4	Tumor displaces the brainstem and adjacent cranial nerves.

Table 4. Patients demographics and clinical characteristics

	n=30
Age (year)	47,1±12,5
Gender	
Male	14 (%46,7)
Female	16 (%53,3)
Duration of symptoms (month)	4,5 (0,25-120)
Comorbid disease	6 (%20,0)
Comorbid malignite	3 (%10,0)
Prior surgery	3 (%10,0)
Koos classification	
I	5 (%16,7)
II	18 (%60,0)
III	1 (%3,3)
IV	6 (%20,0)
On alternate days treatment	10 (%33,3)
Tumor Laterality	
Right	19 (%63,3)
Left	11 (%36,7)
Follow up (month)	20 (2-57)

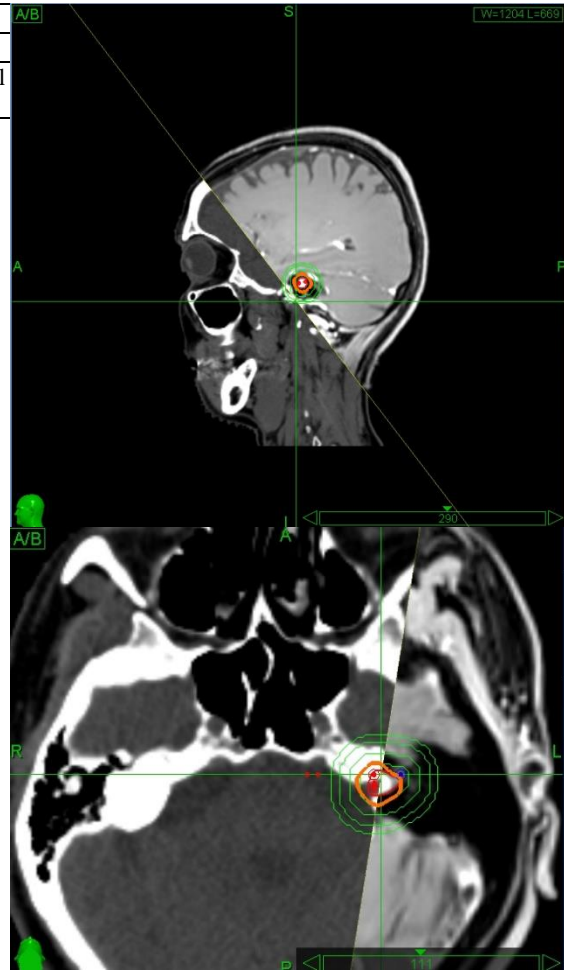


Figure 1. Fused images of a patient treated in 3 fractions

rate was 95.2% at >7-year of follow-up. Overall 4 patients progressed, two assessed with MRI and remaining 2 had clinical deterioration.

Toxicity related to 7th and 8th cranial nerves and cochlea is as important as local control. Patients with VS mostly have unilateral hearing loss as at the time of admission. In the current study, while one patient with initial hearing loss progressed to serviceable hearing after RT, 4 other patients worsened clinically after treatment so that hearing impairment rate was found to be 21% at 21 months follow up. Although pre and post RT change in GR scale was found to be statistically significant this change was not correlated with PTV, Koos Grading and maximal tumor diameter. Baschnagel et al reported that 40 patients with pretreatment serviceable hearing retained hearing 93% in the 1st year, 77% and 73% in 2nd and 3rd years respectively¹⁵. They also observed that hearing impairment was seen more with SRS compared

DISCUSSION

During the median 20 mo follow up, 100% radiologic local control was achieved with statistically significant deterioration of GB and HB scores which could be attributed to treatment related toxicity.

Retrospective evaluation of vestibular schwannoma patients treated with a dose of median 13 Gy gama-knife SRC reported a favorable local control of 97 % in long term follow-up^{9,10}. Conventional doses between 46.8-59 Gy (1.8 Gy/frx) showed similar results^{11,12}. Moreover, Combs et al compared the results of 200 patients treated either with SRS or conventional doses of FSRT and found no statistically significant difference between groups in terms of local control¹³. In a prospective evaluation of 158 VS patients treated with FSRT¹⁴. Patients were treated with received a dose of 50.4 Gy and a safety margin of 1–2 mm was used. The local tumor control

to FSRT but for doses below 13 Gy, toxicity rates are same. The threshold between cochlear dose and hearing dysfunction is not clearly identified but in some SRS studies doses over 4 Gy have been associated with hearing loss¹⁶. We also found no statistically significant correlation between cochlear dosimetry and GR scale alteration. Since toxicity related hearing impairment become evident after 3 years, longer follow up is mandatory.

Due to close proximity, facial nerve is frequently jeopardized. Motor dysfunction is frequent but loss of taste may also become evident. In the study of Combs, fascial toxicity was reported for 4% of 200 patients but it was 17% and 2% for different modalities respectively. We evaluated facial nerve function with pre and post HB scores and found a deterioration which was statistically significant but not correlated with PTV, Coos classification and maximal tumor diameter.

In current study the trigeminal toxicity rate was 6%. In older SRC studies, trigeminal toxicity rates reach to 60% (15-60%)¹⁷⁻¹⁹. The high rates of toxicities have led to a reduction in prescribing doses and in this way a reduction observed in toxicity rates. In 2000 studies, doses prescribed were reduced to 13 Gy and trigeminal nerve protection rates were higher than 95%^{13,20,21}. The trigeminal toxicity rate observed in this study seems to be higher than current studies. One of the patients had VS surgery before RT but others had no known prescribed risk factor. Although there are studies showed that the presence of comorbid disease increasing the risk of developing trigeminal toxicity we could not show a statistically significant association in our series.

CONCLUSION

Due to the lack of randomize controlled study about this subject and the variability of the parameters of these studies, it is difficult to draw definitive results but SRT with CyberKnife seems appropriate for VS treatment in terms of local control and toxicity.

Conflict of interest: The authors declare that they have no conflict of interest

REFERENCES

1. Tos M, Stangerup SE, Cayé-Thomasen P, Tos T, Thomsen J: What is the real incidence of vestibular schwannoma? *Arch Otolaryngol Head Neck Surg* 130:216-220, 2004
2. Stangerup SE, Cayé-Thomasen P. Epidemiology and natural history of vestibular schwannomas. *Otolaryngologic Clinics of North America* 2012;45(2):257-68.
3. Chaimoff M, Nageris BI, Sulkes J, Spitzer T, Kalmanowitz M: Sudden hearing loss as a presenting symptom of acoustic neuroma. *Am J Otolaryngol* 20:157-160, 1999
4. Hansasuta A, Choi CYH, Gibbs IC, Soltys SG, Tse VCK, Lieberman RE, et al. Multisession stereotactic radiosurgery for vestibular schwannomas: single-institution experience with 383 cases. *Neurosurgery* 2011;69(6):1200-9).
5. Varughese JK, Breivik CN, Tore WL, Morten LJ. Growth of untreated vestibular schwannoma: a prospective study. *Journal of Neurosurgery* 2012;116(4):706-12.
6. Dario Muzevic, Jelena Legcevic, Bruno Splavski, Per Cayé-Thomasen. Stereotactic radiotherapy for vestibular schwannoma. *Cochrane Database of Systematic Reviews* 2014, Issue 12.
7. Leksell L: A note on the treatment of acoustic tumours. *Acta Chir Scand* 137:763-765, 1971)
8. House, J.W., Brackmann, D.E. Facial nerve grading system. *Otolaryngol. Head Neck Surg.* [93] 146-147. 1985
9. Boari N, Bailo M, Gagliardi F, Franzin A, Gemma M, del Vecchio A et al. Gamma Knife radiosurgery for vestibular schwannoma: clinical results at long-term follow-up in a series of 379 patients. *J Neurosurg.* 2014 Dec;121 Suppl:123-42
10. Lunsford LD, Niranjana A, Flickinger JC, Maitz A, Kondziolka D. Radiosurgery of vestibular schwannomas: summary of experience in 829 cases. *J Neurosurg.* 2013 Dec;119 Suppl:195-9.
11. McClelland S, Gerbi BJ, Higgins PD, Orner JB, Hall WA. Safety and efficacy of fractionated stereotactic radiotherapy for acoustic neuromas. *J Neurooncol.* 2008 Jan;86(2):191-4. Epub 2007
12. Andrews DW, Werner-Wasik M, Den RB, Paek SH, Downes-Phillips B, Willcox TO et al. Toward Dose Optimization For Fractionated Stereotactic Radiotherapy For Acoustic Neuromas: Comparison Of Two Dose Cohorts. *Int J Radiat Oncol Biol Phys.* 2009 Jun 1;74(2):419-26
13. Combs SE, Kano T, Schulz-Ertner D, Huber PE, Debus R. Differences In Clinical Results After Linac-Based Single-Dose Radiosurgery Versus Fractionated Stereotactic Radiotherapy For Patients With Vestibular Schwannomas. *Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 1, pp. 193-200, 2010*
14. Litre F, Rousseaux P, Jovenin N, Bazin A, Peruzzi P, Wdowczyk D et al. Fractionated stereotactic radiotherapy for acoustic neuromas: A prospective monocenter study of about 158 cases. *Radiotherapy and Oncology* 106 169-174, 2013
15. Baschnagel AM, Chen PY, Bojrab D, Pieper D, Kartush J, Didyuk O et al. Hearing preservation in



- patients with vestibular schwannoma treated with Gamma Knife surgery. *J Neurosurg.* 2013 Mar;118(3):571-8.
16. Benghiat H, Heyes G, Nightingale P, Hartley A, Tiffany M, Spooner D et al. Linear Accelerator Stereotactic Radiosurgery for Vestibular Schwannomas: A UK Series. *Clinical Oncology xxx* (2014) 1-7
 17. Foote RL, Coffey RJ, Swanson JW, Harner SG, Beatty CW, Kline RW, et al. Stereotactic radiosurgery using the gamma knife for acoustic neuromas. *Int J Radiat Oncol Biol Phys* 1995;32:1153–1160.
 18. Suh JH, Barnett GH, Sohn JW, Kupelian PA, Cohen BH. Results of linear accelerator-based stereotactic radiosurgery for recurrent and newly diagnosed acoustic neuromas. *Int J Cancer* 2000;90: 145–151.
 19. Flickinger JC, Lunsford LD, Linskey ME, Duma CM, Kondziolka D. Gamma knife radiosurgery for acoustic tumors: Multivariate analysis of four year results. *Radiother Oncol* 1993;27:91–98.
 20. Myrseth E, Møller P, Pedersen PH, Vassbotn FS, Wentzel-Larsen T, Lund-Johansen M. Vestibular schwannomas: clinical results and quality of life after microsurgery or gamma knife radiosurgery. *Neurosurgery* 56:927-935; discussion 927-935, 2005.
 21. Fukuoka S, Takanashi M, Hojyo A, Konishi M, Tanaka C, Nakamura H. Gamma knife radiosurgery for vestibular schwannomas. *Prog Neurol Surg* 2009; 22:45–62.