Original Article

Evaluation of volumetric and morphological changes of vestibular schwannomas following CyberKnife therapy

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ABSTRACT

Objectives: This study aims to evaluate volumetric and morphological changes following CyberKnife radiotherapy of vestibular schwannomas.

Patients and Methods: Between March 2011 and December 2013, a total of 39 patients (15 males, 24 females; mean age 52 years; range, 19 to 86 years) who underwent CyberKnife hypofractionated radiotherapy were retrospectively analyzed. Tumor volume calculations were done by manual segmentation. Tumor morphology was classified by arbitrary cystic scaling. Local tumor control, tumor progression, transient swelling rates, and changes in tumor morphology were evaluated.

Results: Local tumor control and transient swelling rates were 87% and 46%, respectively. Cystic tumors responded better than solid tumors to treatment as evidenced by volume reduction rates (87% vs. 58%), although local control rates were not significantly different (93% vs. 83%). Transient swelling rates were significantly higher in cystic tumors than in solid tumors (67% vs. 29%). Post-treatment volume changes were not correlated with gender, age group, or pre-procedural tumor volume.

Conclusion: CyberKnife radiotherapy is an effective way of achieving local tumor control in patients with vestibular schwannomas. Although higher rates of volumetric regression would be expected in more cystic tumors than more solid tumors, local control rates are similar.

Keywords: CyberKnife, hypofractionated stereotactic radiotherapy, vestibular schwannoma.

Vestibular schwannomas (VSs) are benign neoplasms located in the cerebellopontine angle and originate from the vestibular branch of the eighth cranial nerve. Among all intracranial neoplasms, their prevalence is about 6%.[1] They may be found sporadically or in relation to neurofibromatosis type II (NF2). Smaller tumors may present with tinnitus and larger ones with sensorineural hearing loss. Vestibular schwannomas are slowly growing tumors and they enlarge about 1 to 2 mm per year.[2]

Treatment options include watchful observation, surgical removal, and stereotactic radiotherapy.[1-6] Due to the benign nature of the tumor, non-aggressive management strategies are preferred. Stereotactic radiotherapy and

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radiosurgery have proven themselves as non-invasive and effective treatment methods for VSs in the last decades. Local tumor control rates using these methods are up to 95%.[3-6]

Magnetic resonance imaging (MRI) is the method of choice in the post-treatment examination of tumor volume and morphology in VS patients. In routine practice, tumor volume is evaluated by measurements of maximal tumor diameters in three planes. However, this method may not represent the actual tumor volume, particularly in tumors with irregular shapes. On the other hand, manual segmentation is an alternative method which has proven to be more precise, although it is more time-consuming.[7-9]

Several studies were previously published in which the volume measurements were made using manual segmentation and computer-assisted area-based calculations.[10,11] While these studies focused mainly on volumetric changes, but not much on morphological changes, we aimed to address into both issues in the present study. Therefore, we aimed to evaluate volumetric and morphological changes of VS using manual segmentation on MRI images following CyberKnife radiotherapy to shed further light into the literature regarding post-treatment VS evaluation.

PATIENTS AND METHODS

Between March 2011 and December 2013, a total of 39 patients (15 males, 24 females; mean age 52 years; range, 19 to 86 years) who underwent CyberKnife hypofractionated radiotherapy were retrospectively analyzed. Pre-treatment and follow-up images between 2011-2015 were retrospectively recruited from the Picture Archiving and Communication System (PACS) of Katip Çelebi University İzmir Atatürk Training and Research Hospital. *Inclusion criteria were as follows:* the presence of a pre-treatment and at least one follow-up contrast-enhanced three-dimensional (3D) gradient-echo (GRE) T1-weighted (T1) MRI study with voxel dimensions of 1 mm^3 for the volume measurement, and also the presence of T1, T2, fluid-attenuated inversion recovery (FLAIR) images for morphological evaluation. Follow-up imaging was not done according to a particular schedule, but rather according to the referring clinician's order. A written informed consent was obtained from each patient. The study was approved by the Katip Çelebi University İzmir Atatürk Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Magnetic resonance imaging studies were performed on a 1.5 Tesla scanner (Signa Excite, General Electric, Milwaukee, WI, USA) using standard sequences as well as contrast-enhanced 3D GRE T1 sequences with a spatial resolution of 1 mm^3 and 512*512 matrix size (BRAVO). A total of 120 scans were examined by a single radiologist and tumor volumes were computed by manual segmentation and volume rendering using the OsiriX V6.5.1 software (Pixmeo SARL266 Rue de BernexCH-1233, Bernex, Switzerland) (Figure 1).

When the tumor volumes in the initial and final scans were compared, a decrease or an increase up to 20% in the tumor volume compared to baseline was defined as local tumor control. Tumor progression was defined as a tumor volume increase of ≥20% of the initial volume. Transient swelling was defined as a tumor volume increase in the first follow-up

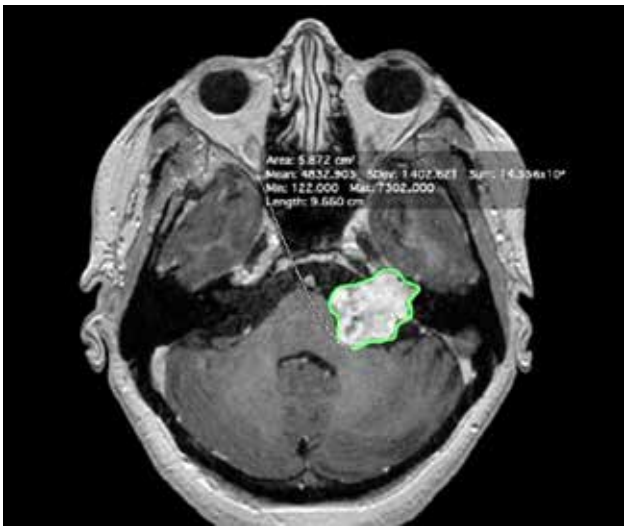

Figure 1. *Each tumor was manually delineated and volume calculation was done using OsiriX software. This process takes few minutes for each tumor depending on complexity of the tumor shape.*

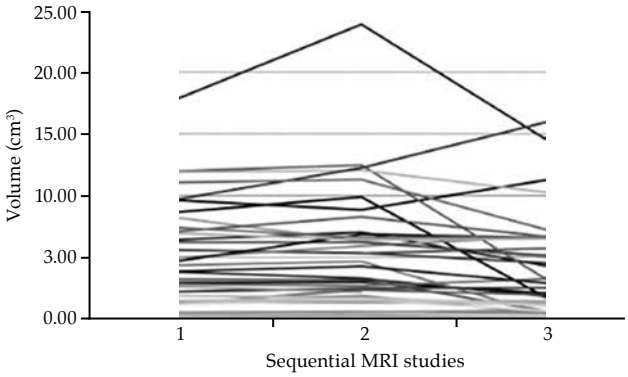

Figure 2. *A graph showing volume changes of tumors on first and follow up scans. Most tumors show a substantial amount of volume increase due to transient swelling, not due to progression.* *MRI: Magnetic resonance imaging.*

scan, which decreased below the initial volumes in the final scan. Tumoral morphological changes during follow-up scans were also recorded. In order to simplify, we arbitrarily categorized tumors on a synthetic scoring from 0 to 3 (0= near totally solid, 1= less than one-third of the tumor is cystic, 2= between one-third to two-third of the tumor is cystic, 3= near totally cystic). The CyberKnife therapy was performed with 1 to 7 fractions with a mean total conformal dose of 18.67 Gy.

Statistical analysis

Statistical analysis was performed using the statistical software R version 3.2.0 (GNU General Public License). Data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. The t-test and Fisher exact test were used to analyze data. A *p* value of <0.05 was considered statistically significant.

RESULTS

The mean follow-up was 25.9 months (range, 6 months to 3 years). Eleven patients had a history of surgery prior to CyberKnife. One patient who was diagnosed with NF2 and had bilateral VS received CyberKnife therapy for one of the tumors.

Table 1. Post-treatment results depending on volume change after final scan

	Volume	Patients
Progression		
Increase	>20%	5
Local control		
Increase	Up to 20%	7
Decrease		27

The mean pre-treatment tumor volume was 4.75 (range, 0.13 to 17.88) cm^3, while the mean post-treatment tumor volume was 3.88 (range, 0.11 to 15.97) cm^3 (Figure 2). There was no significant difference in the mean tumor volume before and after treatment (p=0.3382).

Only five patients showed tumor progression, whereas local control was achieved in 34 patients (87%) (Table 1). No significant difference was found between the patients with tumor progression and those with local control in terms of gender (p=0.785), age (those older vs. younger than 52 years of age) (p=0.298), or tumor volume (those with an initial tumor volume of less or more than 2 cm^3) (p=0.803).

Of 27 patients with decreased volume in the final scan, 18 (67%) showed an increased volume in the first follow-up scan, compatible with transient swelling. This phenomenon was seen in 46% of the patients (18/39). The transient swelling rate was 67% in cystic tumors and 29% in solid tumors, indicating a statistically significant difference (p=0.0448).

CyberKnife radiotherapy made tumors more cystic (Table 2, Figure 3). Tumors with cystic components (type 1 and 2) showed significantly higher volume regression after radiotherapy,

Table 2. Tumoral morphological types and changes in morphology after final scan

	Solid (Type 0)	$^1/_3$ Cystic (Type 1)	$^2/_3$ Cystic (Type 2)	Cystic (Type 3)	Total
Initial scan	24	12	3	0	39
Final scan	14	15	4	6	39

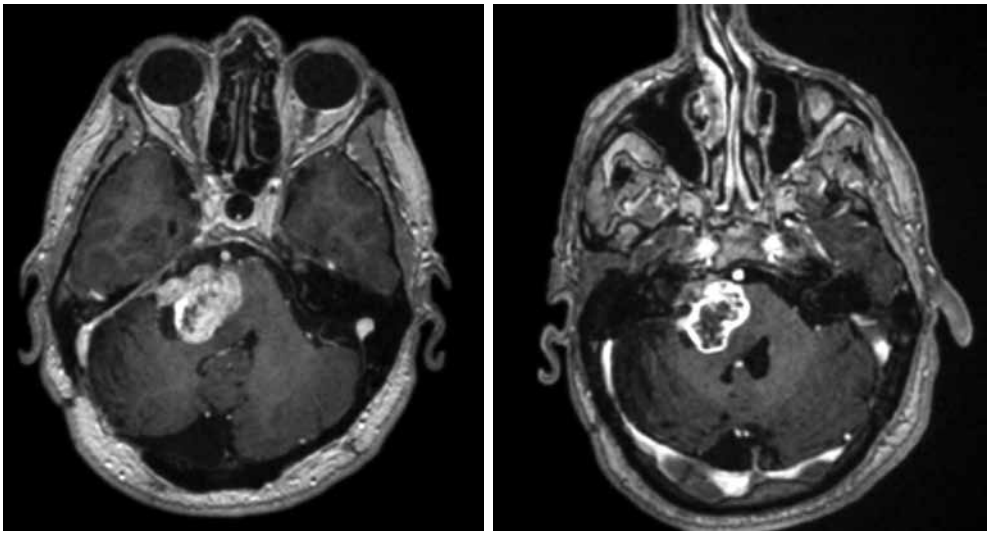

Figure 3. *Three-dimensional, T1-weighted, fast spoiled gradient echo images demonstrating a tumor having type 1 appearance becoming more cystic (Type 3) after CyberKnife radiotherapy on final magnetic resonance imaging scan.*

compared to solid tumors (type 0) (87% vs. 58%, p=0.0112). However, no significant difference was found in the local tumor control rates between the two groups (93% vs. 83%, p=0.6309).

DISCUSSION

In this study, we evaluated local control and transient swelling rates as well as volumetric and morphological changes in VSs following CyberKnife radiotherapy after a mean follow-up of 26 months. We found similar local control rates to those reported in the literature. However, the transient swelling rates were lower than those described in some of the previous studies.[3-6] We also evaluated the morphological changes of tumors during the treatment and found that the tumors became more cystic during the treatment and that initially more cystic tumors showed a higher rate of volume regression, compared to more solid ones.

Considering the tumor size and follow-up volume changes, most of the studies have shown that larger tumors may have a better response to radiotherapy.[12,13] Lederman et al.[13] reported that the size reduction rate was 61% in tumors smaller than 3 cm, and 81% in tumors larger than 3 cm. In another study by Luetje[14] six spontaneous involutions were seen among 47 patients who were conservatively followed. Those tumors with spontaneous involution were noted to have larger sizes, compared to the ones which progressed or remained stable. In our study, the tumor size was not found to be correlated with response to treatment. We compared the volumetric changes before and after treatment in tumors smaller than 2 cm^3 with those larger than 2 cm^3 and found no significant difference. This discrepancy with the literature can be, in part, explained by the cut-off point chosen in our study. We had only six cases under 1 cm^3 and, therefore, the cut-off point was determined as 2 cm^3. Another reason for this discrepancy could be the relatively shorter follow-up period in our study.

There is no consensus on the definition of local tumor control. Some authors have considered stabilization or regression of the tumor size, while some others have defined it as the absence of need for any intervention.[3-9] Meijer et al.[11] defined the tumor progression as an increase in the tumor volume more than 13% compared to baseline, while whereas the threshold for tumor progression was 20% in the study of Okunaga et al.[10] In our study, we chose the cut-off value for progression as 20%. In their study, Okunaga et al.[10] and Meijer et al.[11] found the progression rates to be 19% and 15.6%, respectively. In our study, this rate was 15%, which is similar to the latter. In addition, several studies reported

local control rates of higher than 90%.[3-6] In our study, local control rate was 87%, consistent with previous studies. Indeed, local control rates may vary depending on the length of the follow-up period due to the transient swelling phenomenon. According to previous studies, transient swelling was present in 25 to 62% of the tumors treated with radiotherapy.[15,16] In a study carried out by Meijer et al.,[11] the median follow-up time to have regression of tumors with transient swelling was 34 months. Thus, if the follow-up period is not long enough, some tumors that would eventually regress would be mistakenly classified as progressing tumors. We believe that the relatively shorter follow-up period in the present study did not influence the local control rate, since it is comparable to previous studies.

The definition of the transient swelling is controversial in the literature. Some authors define it as regression of the tumor volume after progression, compared to the previous study, while some others compare it with the initial baseline study rather than the previous one. We used the latter definition in our study and found the transient swelling rate to be 46%, consistent with some of the previous studies.[11,15-17]

For the tumor size evaluation, conventional orthogonal measurements are used widely. Ellipsoid method which can be calculated with multiplication of maximal tumor diameters on x, y, and z axes and division by two is commonly used in studies and in daily practice of radiology. There are manual, semiautomatic, and automatic segmentation methods for volume measurements. Automatic methods require sophisticated and strict MRI protocols, whereas two-dimensional methods have low inter- and intra-observer reliability.[7] In the study of Varughese et al.,[8] it was reported that area-based and orthogonal measurement methods could be accepted, while manual segmentation was reliable, but time-consuming. In our study, we used manual segmentation for reliable volume calculation of the complex-shaped tumors, such as VSs.

In our study, more cystic tumors (type 1 and 2) showed a regression rate of 87% during follow up, which was significantly higher, compared to the regression rate of more solid tumors (type 0 to 58%). The transient swelling rate was 67% in cystic tumors and 29% in solid tumors, indicating a statistically significant difference (p=0.04). On the contrary, in a study by Mohammed et al.,[18] with a small cohort of 18 patients with volume calculations done by manual segmentation, no significant difference was found between the results based on the tumor sizes after fractionated stereotactic radiotherapy in cystic versus solid tumors. In a study by Nakamura et al.,[19] based on gamma radiosurgery in which volume calculations were done using the ellipsoid method, the authors showed cystic tumors to have a better response than solid tumors and have a tendency to show more prominent volume change over time. The authors also underlined that some cysts had fluid-fluid levels on follow-up images, which might be due to microhemorrhages of the cyst walls following radiation exposure. Additionally, on histological examinations of the surgical specimens, which had previous radiotherapy, hyalinized thrombosis, vascular wall thickening, occlusions, and granulomatous changes were observed. Similarly, the cystic conversion of the tumor stroma in some of our cases may be related to necrosis or microhemorrhages, as described by these authors. Although our findings showed that initially cystic VSs tended to respond better to CyberKnife radiotherapy for volume regression, they did not significantly differ from more solid tumors in terms of the local tumor control rates. Tumors may show transient swelling, and that effect is more prominent in cystic tumors, which correlates with the gamma knife-based study of Nakamura et al.[19]

The main limitations of our study include the relatively short follow-up period, the lack of a standardized follow-up imaging schedule, and relatively small sample size.

In conclusion, our study findings indicate that if the tumor volume shows regression in the first follow-up imaging, one may assume that local control would be achieved eventually. Even in cases with an increased tumor volume in the first imaging study, the probability for local control is high, since this is usually due to the transient swelling phenomenon. Although the literature data suggests a relatively longer follow-up duration to accurately evaluate tumor

progression versus local control, shorter follow-up in our study allowed us to achieve comparable local control rates with previous studies. One should keep in mind that, in more cystic tumors, a higher rate of volumetric regression and a higher likelihood of transient swelling would be expected in response to CyberKnife therapy, compared to more solid tumors.

Declaration of conflicting interests

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