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Early magnetic resonance image volumetric changes of vestibular schwannoma after Gamma Knife radiosurgery: a prospective study of 18 cases

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Abstract

Background: Gamma Knife radiosurgery is the principal alternative to microsurgical resection for acoustic neuromas (vestibular schwannomas). However; its increasing use worldwide and evolution of Gamma Knife device precision and safety had led to its acceptance as primary management for small- and medium-sized vestibular schwannomas. We tried to evaluate the tumor volume changes that occur with these tumors following Gamma Knife radiosurgery.

Methods: Eighteen patients with stereotactic radiosurgery with Gamma Knife through the year 2016 completed 1-year MRI follow-up at the 3rd, 6th, and 12th month after the Gamma Knife treatment. All the patients had unilateral vestibular schwannomas; the mean dose of radiation to the tumors was 12 Gy (range 10–14 Gy). Post treatment imaging was done with a high-resolution 3 T MRI scanner. Tumor sizes are calculated by using Onis software.

Results: Four patterns of volumetric changes were noticed. Most of the tumors increased in size on the third month follow-up MRI (89%); 15 (83%) tumors on the sixth month returned to their initial pre-Gamma Knife radiosurgery (PGKR) sizes. On the last (12th month) follow-up MRI with tumor sizes compared to initial PGKR sizes, 8 (44%) tumors showed no change, 6 (33%) tumors became smaller, and 4 (22%) tumors increase in size. Tumor control rate was 78% for the first year after Gamma Knife radiosurgery.

Conclusions: The third month follow-up MR images are practically not informative and might lead to unnecessary intervention; sixth month follow-up MR images are a crucial point and they may predict tumor behavior. Age, gender, and Koos stage whether stage II or III are not affecting tumor control. Gamma Knife radiosurgery is an effective intervention for Koos II and Koos III vestibular schwannomas.

Keywords: MRI volumetric changes, Vestibular schwannomas, Gamma Knife

Background

Vestibular schwannoma (VS) accounts for 5–8% of intracranial tumors and 80–90% of cerebellopontine angle tumors [1]. They are used routinely to measure tumor size. They are bilateral in about 4–5% of cases. Vestibular schwannoma occurs most frequently in middle age.

They arise near the transition point between glial and Schwann cells, known as the Obersteiner-Redlich zone, which occurs near or at the porous acoustics [2]. The natural history of tumor growth is variable, whereas some lesions demonstrate continuous growth and others grow to a certain size and stagnate or even shrink [3].

Sughrue et al. found among 982 patients the mean initial tumor size was 11.3 mm, and the average growth rate was 2.9 ± 1.2 mm per year [4]. VS are classified as World Health Organization Grade I tumors. Unlike neuromas, they are well-circumscribed, encapsulated lesions that splay rather than invade adjacent nerve fibers [5].

The earliest and most frequently reported symptom is hearing loss. Because of the episodic nature, slow time course, and patient adaptation, it is not unusual for symptoms to be neglected for an extended period before presentation [6].

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Computer tomography (CT) and magnetic resonance imaging (MRI) classification systems are in current usage, and none are universally 54 55 accepted [7, 8]. Tumors have been classified by Pulec et al. [9] into three groups: small (intracanalicular), medium (extending beyond the internal meatus but by < 2.5 cm), and large (> 2.5 cm). Koos [10] classification is more widely used (Table 1).

In the First International Conference on Acoustic Neuroma, however, Tos and Thomsen [11] made a plea that the following classification be adopted universally so that reporting of results could be standardized. They have proposed that the intra-meatal component (usually about 1–1.5 cm) should not be included in the measurement. Size instead is measured as the largest extra-meatal diameter. Tumors are classified as intra-meatal, small (1–10 mm), medium (11–25 mm), large (26–40 mm), and extra large (> 40 mm).

It appears likely that, with the advent of computerized three-dimensional reconstruction imaging, tumor volume, rather than maximum diameter, will ultimately become the measurement upon which these lesions are graded [12]. The natural history of these incidentally found lesions must be weighed against the potential morbidity associated with treatment [13, 14].

Gamma Knife stereotactic radiosurgery (SRS) was first used in 1969 by Leksell to treat VS [15]. Since the 1990s, microsurgery and SRS have become well-established management options for VS [16]. The best candidates for radiosurgery are young patients with small- and middle-sized VS and few symptoms. Patients with Koos stage II and III tumors are good candidates as well.

In this study, we tried to evaluate the tumor morphological changes that occurred in the context of tumor volume during the first year of treatment.

Methods

This is a clinical prospective study of 18 patients with vestibular schwannomas treated with Gamma Knife radiosurgery in the Gamma Knife Radiosurgery Center (Leksell Gamma Knife PERFEXION), Neurosciences Hospital, Baghdad.

They completed 1-year follow-up at the 3rd, 6th, and 12th month after the Gamma Knife treatment and were evaluated consequently with a scheduled MRI. All of them had unilateral vestibular schwannomas, with no previous surgery or recurrent tumors.

Table 1 Koos classification system

Grade	Definition
1	Intracanalicular
2	Tumor in the cerebellopontine angle but not reaching the pons
3	Tumor reaching the pons, perhaps deforming it but not shifting it
4	Tumor deforming the pons and shifting the fourth ventricle

Patients' ages ranged from 17 to 70 years (mean, 52 years). Eight were male (44%), and ten were female (56%). Tumors were Koos stage II (8 cases, 44%), Koos stage III (8 cases 44%), and Koos stage IV (2 cases 22%). Thirteen were on the right side and five on the left side. Tumor sizes ranged from 0.3 to 14.8 cm^3 (mean 4.2 cm^3).

Gamma Knife treatment

All patients were admitted on the morning of the day of the procedure and discharged few hours after Gamma Knife radiosurgery, except for one who developed moderate hydrocephalus after 2 days of treatment and was admitted for 4 days, and hydrocephalus subsided conservatively during admission. Stereotactic localization was achieved with Leksell fixation, frame type G. The frame is fixed to the patient's skull under local anesthesia. The frame fitting cap is applied to check the fitness of the frame. The scalp of the patient's head is measured manually using the ruler with a skull-scaling device. We used a high-resolution 3 Tesla MRI scanner (Philips Achieva). The images were T1W with contrast and T2W, in slice thickness of 1 mm and three planes (axial, coronal, sagittal). The plan was exported into the treatment-planning system via an intranet. The target (VS) is delineated with Gamma Plan software.

Treatment planning and dose prescription

A dose plan is rendered to deliver an ideal dose to the target and a safe dose to adjacent eloquent structures. Various parameters, such as dose-volume histograms for the target volume and critical structures, are obtained and outlined. Also, conformity, dose uniformity, and gradient index are assessed, and adjustments are made to optimize the treatment plan. A single-session radiosurgery uses a dose range of 10–14 Gy (mean 12 Gy). We used the 50% isodose line to cover the margin of the tumor. This means the tumor margin will receive 50% of the maximum dose in the target (Fig. 1). All the radio surgical data is exported to the operating console, which is used to control and monitor the patient treatment procedure.

Patients had follow-ups at 3, 6, and 12 months after treatment with the same protocols used during Gamma Knife treatment. Imaging was obtained by the same MRI scanner.

Tumor size calculation

For data documentation and manual calculation of tumor size, we used a software program (Onis viewer and server) which is a professional DICOM viewer (Fig. 2). The size is more sensitive than the maximum diameter (of slice where the tumor appears the largest) in detecting tumor

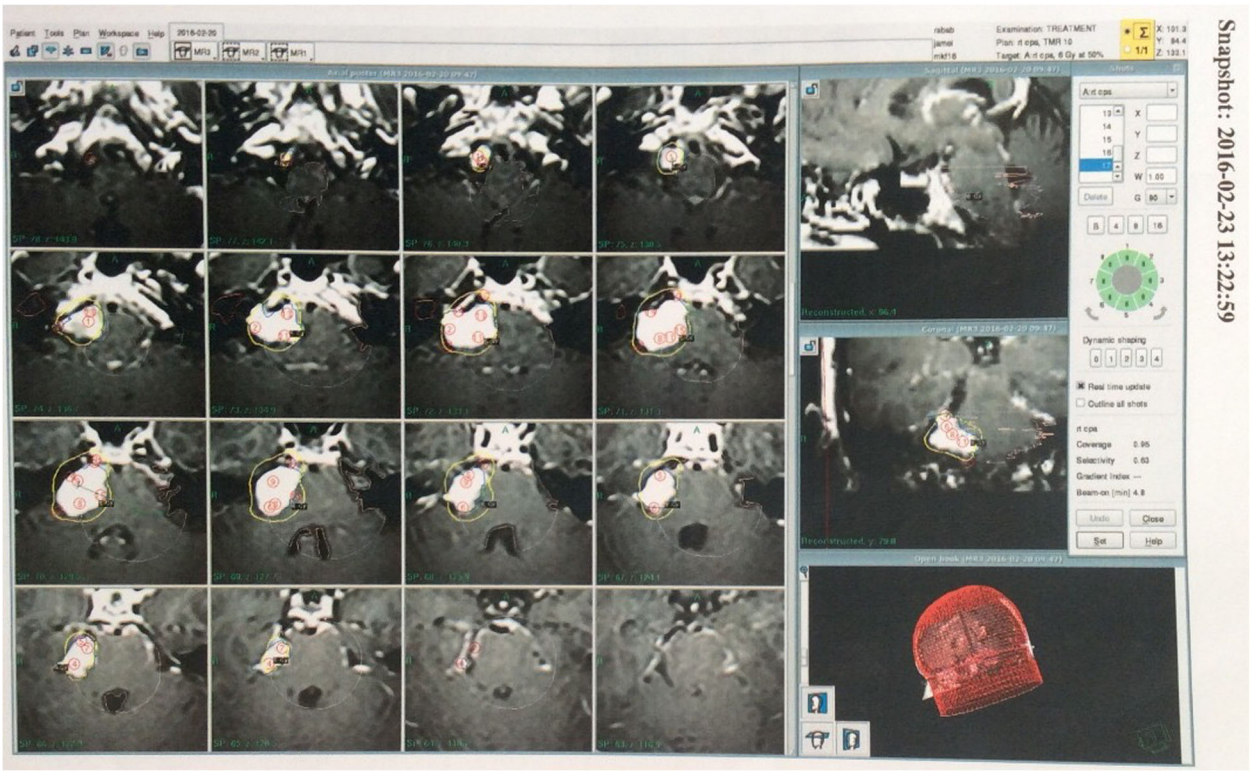

Fig. 1 Surgiplan platform for VS tumor

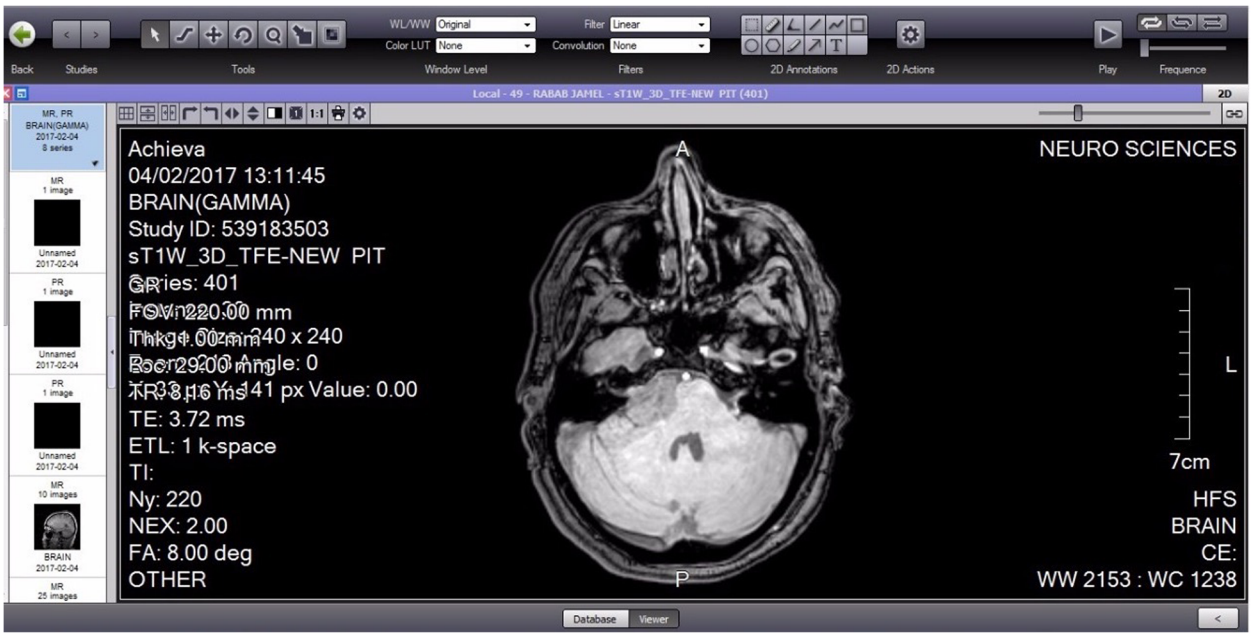

Fig. 2 Onis viewer software used to measure tumor diameters

volumetric changes. We used Petersen and Espersen formulas [17] to calculate the size by identifying the T1W axial slice with the most major area of the tumor. Measure the maximum diameter in this section, (A diameter); the maximum diameter orthogonal to (A), (B diameter); and the number of sections in which that tumor appears (1 mm of each one) or the maximum sagittal height, (C diameter) with either no change in size or regression. A *t*-test is used to compare

$$\text{The size of tumors} = A * B * C/2.$$

Also, since we used the same protocols of MRI during the follow-up period, the images were coregistered to evaluate whether really there were changes in volume or not, but we used the ABC/2 to have a numerical value for this change.

Tumor size changes and statistics

Tumor sizes at each follow-up image (3, 6, and 12 months) were compared to those at pre-Gamma Knife radiosurgery (PGKR). Tumor control rate is estimated by comparing tumor size at the time of treatment with that at the last follow-up (12 months). We used Vokurka et al.'s [18] rule that a volume change of more than 13% is considered an increase (progression) or a decrease (regression) in size. A tumor is regarded as controlled if it shows changes that occurred in the same group after the intervention, and P values < 0.05 are considered significant.

Results

The tumor size measurements with the size changes on the 3rd, 6th, and 12th months of follow-up MR images are summarized in (Table 2).

Three-month follow-up MRI tumor size changes

All 18 tumors showed increases in size on the 3-month follow-up MRI. The PGKR sizes ranged 0.3–14.8 cm^3 (mean 4.26 cm^3). After 3 months of treatment, the volume reached 0.34–18.5 cm^3 (mean 5.22 cm^3). The average tumor size increase was 0.96 cm^3 (22.5%) (Fig. 3).

The 16 tumors size differences between PGKR and the 3-month follow-up are significant (t-test = 0.0003, $P < 0.05$).

Six-month follow-up MRI tumor size changes

A total of 15 tumors returned to amounts near their first PGKR sizes (i.e., within the range of ± 13% of original PGKR sizes). PGKR tumors sizes ranged from 0.3 to 14.8 cm^3 (mean 4.26 cm^3).

The 6-month follow-up MRI tumor volumes reached 0.325–18.35 cm^3 (mean 4.86 cm^3) (Fig. 4).

The mean increase in tumors sizes was 0.3 cm^3 (7. 18%) (t-test = 0.057, $P > 0.05$). Three tumors showed an increased in size in comparison to their first PGKR sizes,

Table 2 Detailed patient data

Patient characteristics			Tumor characteristics			Follow-up MRI size (cm^3)		
Patient No.	Gender	Age (year)	Koos classification	Side	PGKR size (cm^3)	3 months	6 months	12 months
No.I	Male	50	II	Right	0.30	0.345	0.325	0.275
No.2	Male	60	II	Right	0.86	1.12	0.91	0.75
No.3	Female	54	II	Left	1.01	1.35	1.05	1.05
No.4	Male	60	III	Left	6.91	8.9	7.55	7.05
No.5	Female	56	IV	Right	3	3.85	3.2	3.3
No.6	Female	40	III	Right	2.85	3.55	3.15	3.1
No.7	Male	17	III	Left	10.23	11.8	13.15	17.25
No.8	Female	70	III	Right	9.43	11.35	9.55	10.95
No.9	Female	70	II	Right	2.88	4	3.15	2.35
No.10	Male	35	III	Right	1.28	1.52	1.3	1.3
No.II	Female	39	III	Right	6.55	7.59	7	5.05
No.12	Female	67	II	Left	1.67	1.93	1.8	1.75
No.13	Male	63	III	Left	4.14	4.5	4.5	3.6
No.14	Male	53	III	Right	14.8	18.55	18.35	15.2
No.15	Female	48	II	Right	1.05	1.2	1.25	1.4
No.16	Female	35	II	Right	1.32	1.39	1.3	1
No.17	Male	31	II	Right	1.6	2.2	1.45	1.1
No.18	Female	34	IV	Right	6.86	8.87	8.5	9.6

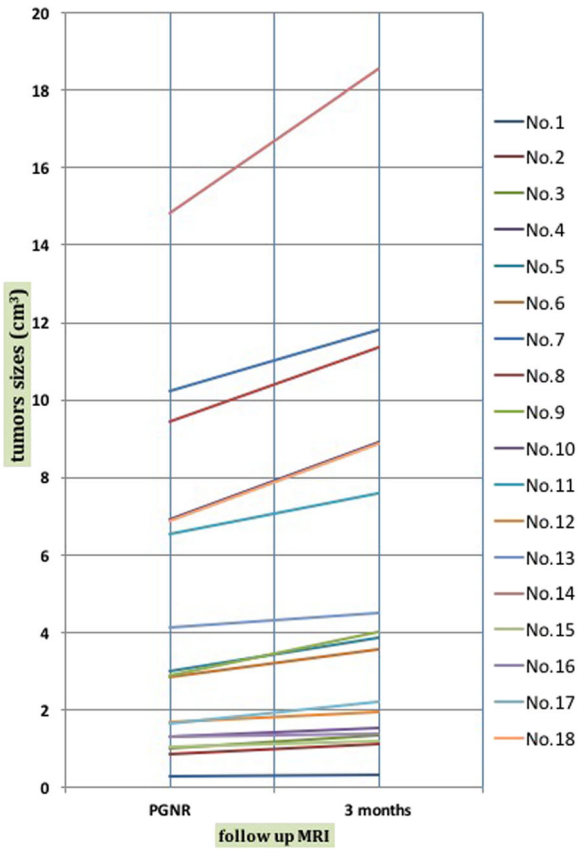

Fig. 3 Linear chart show tumors volumetric changes after 3 months of GNRS

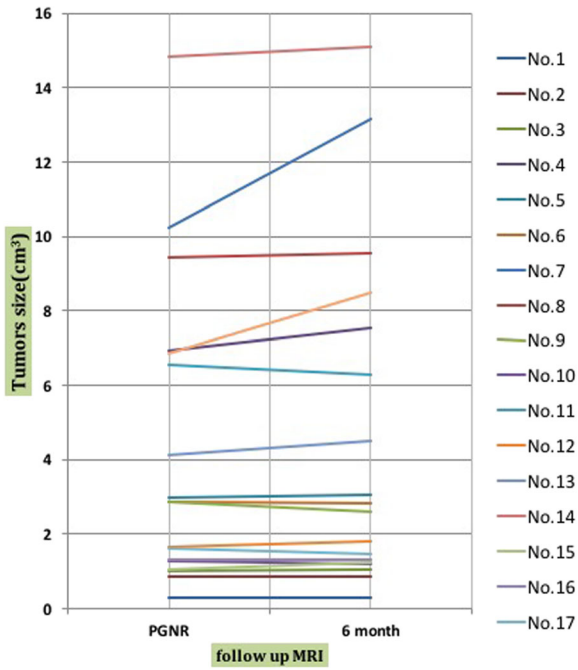

Fig. 4 Linear chart shows tumors volumetric changes after 6 months of GNRS

and when compared to their sizes at the 3-month follow-up MRI, one tumor grew more than its 3-month follow-up MRI size.

Twelfth month follow-up MRI tumor size changes

Six tumors (33%) decreased in size (regression) in comparison with their first PGKR sizes. Eight tumors (44%) showed no change in size compared to their original PGKR sizes (i.e., within the range of ± 13% of original PGKR sizes). Four tumors (22%) showed a significant increase in size in comparison with their first PGKR sizes, and three of them steadily increased on the 3- and 6-month follow-up MRIs. One had an increase and then a decrease in size in the 6- and 12-month follow-up MRI, respectively.

PGKR sizes ranged from 0.3 to 14.8 cm^3 (mean 4.26 cm^3). After 12 months (last follow-up), they ranged from 0.275 to 17.25 cm^3 (mean 4.78 cm^3) (Fig. 5).

The mean increase in tumor sizes was 0.51 cm^3 (12%) (t-test = 0.127, $P > 0.05$). In the comparison of tumors' volumetric changes observed on the last follow-up MRI with gender (eight males, ten females) as a variable, we found that the differences were not significant (t-test = 0.45, P value > 0.05).

We compared tumors' volumetric changes on the last follow-up MRI using the Koos classification of VS (8 Koos II, 8 Koos III, 2 Koos IV), and the differences were not significant (t-test = 0.071, P value > 0.05).

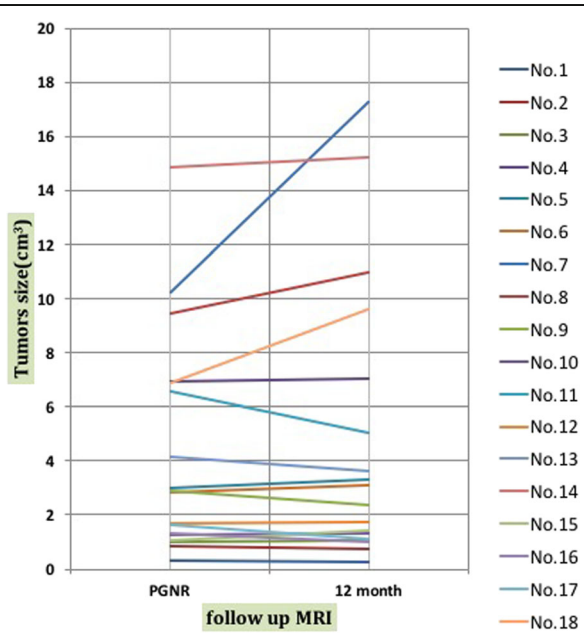

Fig. 5 Linear chart shows tumors volumetric changes after 12 months of GNRS

For the median age (52 years), we compared two groups (above and below 52 years), and the differences were not significant (t-test = 0.19, P value > 0.05).

We recognize that a tumor's behavior after Gamma Knife radiosurgery (GKRS) through the first year divided into four patterns:

Pattern A

Tumor sizes increased over 3 months and returned to their initial PGKR size and then decreased on the 12-month follow-up MRI (regression) (six tumors) (Fig. 6).

Pattern B

Tumor sizes increased over 3 months and returned to their initial PGKR size and then showed no change on the 12-month follow-up MRI (eight tumors) Fig. 7.

Pattern C

Tumor sizes steadily increased on the 3-, 6-, and 12-month follow-up MRI (three tumors) Fig. 8.

Pattern D

The tumor size increases in 3 months, returns to its initial PGKR size, and has increased again by the time of the follow-up MRI 12 months later (one tumor) Fig. 9.

Discussion

In this study, most of the tumors had undergone an increase in size 24 25 by the 3-month follow-up MRI schedule due to the biological effect of radiosurgery on vestibular schwannoma cells [19]. It meant there was an early tumor response to radiation. This progression was not real (pseudoprogression). However, the correct pathological explanation of this phenomenon is still being debated.

Delsanti et al. [20] and Yu et al. [21] studied the volumetric change of VS after Gamma Knife radiosurgery, and they found that most of the tumors enlarged through the first year; the maximum enlargement occurred in the sixth month, which differed from the indications of our study (i.e., enlargement during the third month). Unlike in our study, their follow-up schedule was not for the 3-month mark; pseudoprogression started earlier, and they did not mention the standard dose when the usual maximum radiation dose in that period (1992–2008) was different in Gamma Knife centers (ranging from 11 to 40 Gy with a mean of 16 Gy). As this pseudoprogression was not associated with new clinical symptoms [22], it was important to delay MRI

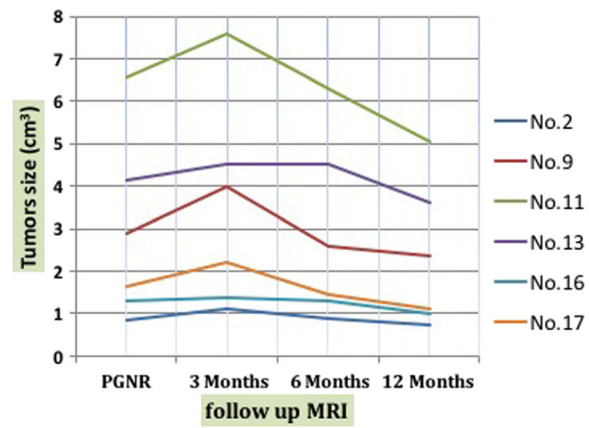

Fig. 6 Linear chart shows pattern A tumors volumetric changes

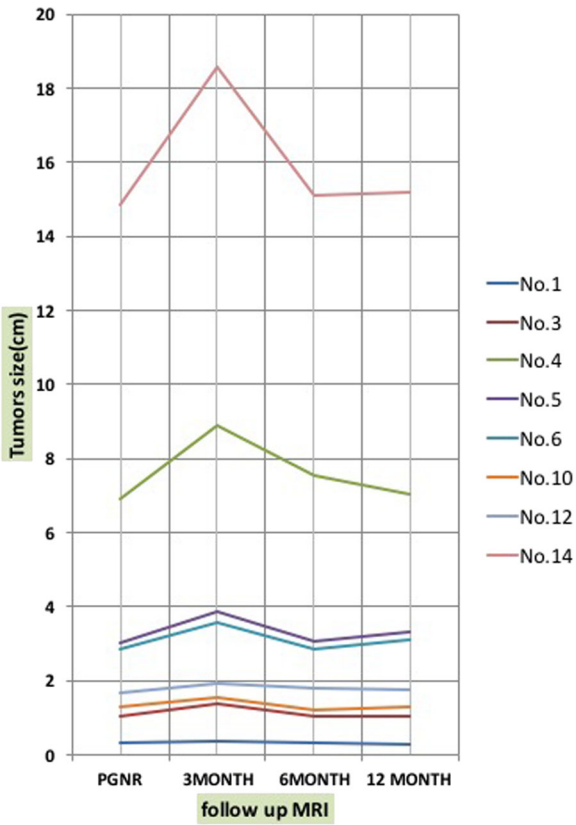

Fig. 7 Linear chart shows pattern B tumors volumetric changes

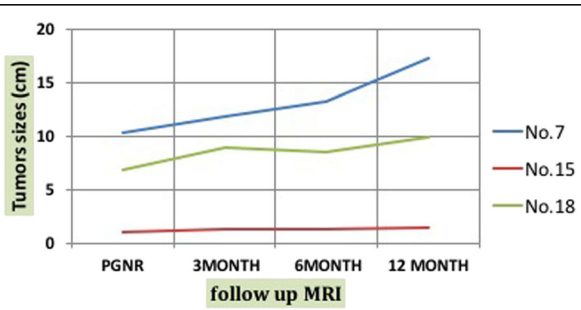

Fig. 8 Linear chart shows pattern C tumors volumetric changes

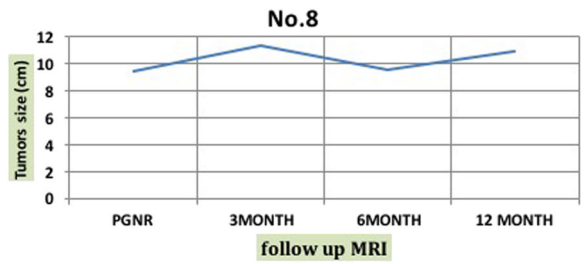

Fig. 9 Linear chart shows pattern D tumor volumetric changes

follow-up for more than 3 months. Hence, this phenomenon is predictable and might lead to unnecessary further intervention. In our study, during the 6-month follow-up MRI, three tumors (17%) showed steady progression. Delsanti et al. and Yu et al. had 54 and 45%, respectively. These differences in our results are supposed to be due to the use of higher doses that led to delayed tumor size specified in the Delsanti et al. and Yu et al. studies. Tumor size returns to their initial PGKR sizes. Tumor control rate was not specified in the Delsanti et al. and Yu et al. studies.

In Nakamura et al.'s study [23], a tumor was controlled if it showed either no change or regression. The tumor control rate is highly dependent on duration where the last follow-up is considered (i.e., the period of study). Although our study was relatively short term and had a small number of patients, the tumor control rate was 78% (patterns A and B).

In Nakamura et al.'s study, the mean of the follow-up period was 34 months, during which the tumor control rate was 81%, which supports our research. In our study, tumor control was not affected by age, gender, and Koos stages.

Four tumors increased by 22%. Three of them had steadily increased volumes on the 6-month follow-up MRI (pattern C). This change indicates that most of the tumors that show progression 6 months after treatment will increase on the last follow-up. This is an important station in MRI follow-ups, but we need more time to consider treatment failure.

Conclusions

The 3-month follow-up MR images after GKRS are practically not informative and might lead to unnecessary interventions and costs. The 6-month follow-up MRI images after GKRS form a crucial point that can predict tumor behavior. Age, gender, and Koos stage (II, III) as variables are not affecting the tumor control rate. Gamma-knife radiosurgery is an effective intervention for Koos II and Koos III vestibular schwannomas.

Abbreviations

DICOM: Digital imaging and communications in medicine; GKRS: Gamma Knife radiosurgery; Gy: Grays (radiation unit); MRI: Magnetic resonance imaging; PGKR: Pre-Gamma Knife radiosurgery; SRS: Stereotactic radiosurgery; VS: Vestibular schwannoma

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Ethics approval and consent to participate

The Baghdad University Ethics Committee approved the study on October 09, 2016 (Ref no. 34122). An informed consent for the treatment was taken from all patients.

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Availability of data and materials

The dataset supporting the conclusions of this article are included within the article.

Authors' contributions

All the authors participated in giving treatment to the patients, filling the data sheets, and writing the manuscripts under the supervision of the corresponding author. All authors read and approved the final manuscript.

Consent for publication

A consent for publication from the patients was not required.

Competing interests

The authors declare that they have no competing interests.

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