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CLINICAL ARTICLE - BRAIN TUMORS

How to distinguish tumor growth from transient expansion of vestibular schwannomas following Gamma Knife radiosurgery

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Abstract
Background Typically, vestibular schwannomas (VS) react to Gamma Knife radiosurgery (GKRS) with a transient increase of tumor volume owed to tumor swelling at about 6 months followed by a reduction of tumor volume owed to tumor shrinkage at about 18 months. It is important to distinguish this transient tumor expansion (TTE) from tumor growth. We undertook this study to see if there is a typical time interval in the follow-up of VS following GKRS, which may indicate tumor growth rather than TTE.
Methods We retrospectively reviewed the patient charts of patients who underwent GKRS for unilateral sporadic VS at the Gamma Knife Center Zurich from 1994–2009 and who were treated by J. Siegfried or one of the authors (TM). Tumor progression was defined as an increase of tumor volume of≥ 20 % as compared to the initial tumor volume at the earliest 2 years following GKRS. This time interval of≥2 years was chosen in order to distinguish TTE from genuine tumor progression. Whenever tumor enlargement was suspected on follow-up MRI at≥2 years following GKRS, tumor volumes were measured using custom software.
Results From 1994–2009, 235 patients underwent GKRS in Zurich for unilateral sporadic VS. Tumor progression with a volume increase of≥20 % occurred in 21/235 (8.9 %) patients at 3.4 ± 0.9 years following GKRS. Seventeen out of 235 (7 %) patients had a clinically relevant tumor progression requiring microsurgery or repeat radiosurgery.
Conclusions According to our data, time may be a good parameter distinguishing tumor progression due to tumor growth from TTE due to tumor swelling in VS following GKRS. Tumor growth seems to occur at about 3–4 years following GKRS for VS as opposed to TTE, which seems to be present at about 6–18 months following GKRS for VS.

Keywords Vestibular schwannoma · Tumor growth · Transient tumor expansion · Tumor enlargement · Radiosurgery

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Introduction

For almost three decades, Gamma Knife radiosurgery (GKRS) has been successfully deployed in the treatment of vestibular schwannomas (VS). Treatment success is defined as tumor control or the absence of tumor progression. Long-term tumor control is achieved in more than 90 % of cases. The vast majority of VS respond to GKRS with a characteristic transient expansion of tumor volume, which has been analyzed and described thoroughly by Nagano et al. [5]. This pathophysiological phenomenon is called transient tumor expansion (TTE) and is believed to be due to radiation-induced tumor swelling. TTE is visible on follow-up MRIs. It is usually associated with a transient loss of contrast enhancement, and in the vast majority of cases it is of no or little relevance to the patient because of its transient nature. Since TTE is a transient phenomenon, it needs to be distinguished from genuine or ongoing tumor progression caused by tumor growth. TTE is a process that starts at about 3 months following GKRS, it peaks at about 6 months, subsiding thereafter and may last for up to 12 or 18 months following GKRS [5]. TTE is characteristic for VS and follows a characteristic time pattern. For unknown reasons, TTE is much less prevalent in other benign tumors such as meningiomas. TTE in VS is independent of age, gender, laterality, previous surgery, tumor volume, peripheral dose, conformity index, and dose rate [5]. As opposed to TTE, tumor progression or tumor growth are synonymous with treatment failure. Tumor progression is a

different pathophysiological phenomenon from TTE caused by tumor growth; it is visible on follow-up MRIs, it is usually not associated with a loss of contrast enhancement, contrary to TTE it is of great relevance to the patient, and it occurs in less than 10 % of VS following GKRS. Little is known about its devolution. There are indications that treatment failure seems to occur at some unknown point in time between 2 and 5 years following LINAC-based radiosurgery for VS [3] and not later than 10 years following GKRS for VS [1]. We undertook this study in order to investigate if there is a typical time interval that may be associated with true tumor progression. To avoid confusing TTE with tumor progression, we added a security margin of 6 months to the 18 months during which TTE may be encountered. Therefore we included into our study only a volume increase that occurred at the earliest 2 years (18 months + 6 months) following GKRS. This study's build-up is based on the hypothesis that TTE and true tumor progression are two distinct phenomena and that they may follow different time patterns.

Materials and methods

We retrospectively reviewed the patient charts of patients who underwent GKRS for unilateral sporadic VS at the Gamma Knife Center Zurich from 1994–2009 and who were treated by one of the authors (TM) or J. Siegfried using a Leksell Gamma Knife Model B (Elekta AB, Stockholm). Inclusion criteria were unilateral sporadic VS undergoing GKRS with a follow-up of at least 2 years. In order to avoid classifying TTE as tumor progression, any tumor enlargement within the first 2 years following GKRS was not considered tumor progression and was not measured since it was assumed that the vast majority was of transient nature. Tumor progression was defined as a measured volume increase of≥20 % compared to the initial tumor volume at the time of GKRS occurring at the earliest 2 years following GKRS that was not followed by tumor shrinkage. Follow-up consisted of MRIs at our institution and appointments with the neurosurgeons who did the GKRS at 6 months, 1,2,3,4,5, and 2-year intervals thereafter. Whenever the neuroradiologists at our institution suspected tumor progression on follow-up MRIs at the 2-year follow-up or later, tumor volumes were measured by one of us (TM) using the custom software Volumseries as published by Scheib et al. [7]. The calculated tumor volume was then compared with the tumor volume at the time of GKRS, which was derived from the planning software Leksell GammaPlan (Elekta AB, Stockholm). The point in time at which a volume increase of≥20 % was observed was considered the moment of tumor progression or tumor growth. Prescription dose refers to the dose at the 50 % isodose and the tumor margin, reference dose to the dose maximum within the tumor, and conformity index to the index published by Lomax and Scheib [2]. Data are presented as mean ± SD. The statistical significance of differences was compared for tumors with no progression and those with progression by the *t* test and Fisher's exact test where appropriate.

Results

From 1994–2009, 235 patients underwent GKRS in Zurich for unilateral sporadic VS. The tumor volumes at the time of GKRS and their respective Koos grading have been published elsewhere [4]. Of the 235 patients, 215 (91.5 %) underwent primary GKRS and 20 (8.5 %) underwent GKRS for tumor recurrence following open microsurgery. Post GKRS follow-up was 5.2 ± 2.75 years. Patient, tumor, and treatment characteristics are listed in Table 1. According to our definition, tumor progression occurred in 21/235 (8.9 %) patients at 3.4 ± 0.9 years following GKRS. Of those 21 patients with tumor progression, 4/21 (19 %) did not require therapeutic action during follow-up. In 17/21 (81 %) patients with tumor progression therapeutic action was required during follow-up. A clinically relevant tumor progression occurred in 17/235 (7 %) patients during follow-up. Eleven (65 %) of those 17 patients underwent microsurgery, 5/17 (29 %) underwent repeat GKRS, and 1/17 (6 %) underwent both repeat GKRS and

Table 1 Patient-, tumor-, and treatment characteristics of 235 patients with VS* undergoing GKRS**

Female (*n*)	122
Male (*n*)	113
Female-to-male ratio	1.08
Age at GKRS (years)	57.3±12.8
Follow-up (years)	5.2±2.75
Microsurgery before GKRS (*n*)	20
GKRS as primary treatment (*n*)	215
Overall tumor volume (cc)	1.85±2.21
Koos grade I (*n*)	32 (0.25±0.30 cc)
Koos grade II (*n*)	71 (0.57±0.54 cc)
Koos grade III (*n*)	70 (1.82±1.88 cc)
Koos grade IV (*n*)	62 (4.17±2.75 cc)
Prescription dose (Gy)	12.9±0.9
Reference dose (Gy)	25.8±1.8
Isocenters (*n*)	10.8±5.8
Conformity index	0.8±0.1
Tumor progression*** (*n*)	21/235 (8.9 %)
Tumor progression*** requiring surgery or repeat GKRS (*n*)	17/235 (7 %)
Time of tumor progression*** (years)	3.4±0.9

* VS = sporadic unilateral vestibular schwannoma

** GKRS = Gamma Knife radiosurgery

*** Tumor progression = persistent volume increase of ≥ 20 % compared to the initial tumor volume at the earliest 2 years following GKRS

microsurgery. Tumor recurrence was statistically independent of age, gender, tumor volume, Koos grade, presence or absence of tumor cysts, prescription dose, and conformity index.

Discussion

Our data are based on volume measurements of VS in the case of suspected tumor progression at the earliest 2 years following GKRS. They are compared with published historical data on TTE [5]. Following GKRS, unilateral sporadic VS typically undergo a volume increase due to tumor swelling caused by radiation effects, which lasts about 6–18 months following GKRS in the vast majority of cases [5]. This typical post-GKRS course with TTE due to tumor swelling must be differentiated from true tumor progression due to tumor growth, otherwise patients are at risk of undergoing unnecessary interventions such as microsurgery or repeat radiosurgery. Therefore, neurosurgeons should be familiar with the changes that VS may undergo following GKRS. So far it has been unclear at what point in time it may be adequate to assume true tumor progression rather than TTE. Our study suggests that an increase of tumor volume due to true tumor progression occurs 3–4 years following GKRS. This is distinctly different from the published time period during that TTE may occur due to tumor swelling. This finding adds one more criterion to the evaluation of treatment success of VS following GKRS. The various patterns of volume increase that may occur in VS following GKRS have been described in detail and illustrated by Pollock [6]. The most common scenario is treatment success or tumor control, which occurs in more than 90 % of the cases and which is accompanied by TTE in more than 70 % of the cases. TTE and tumor progression seem to follow different time patterns, which may allow differentiating them from one another. A limitation of this study is the comparison of its data with historical data. Further research in the field is necessary.

According to our data, a volume increase≥20 %, which occurs at 3–4 years after GKRS, is most likely to be caused by tumor growth and indicates treatment failure. Therefore we recommend waiting for at least 2 years, preferably 3–4 years in the case of suspected tumor progression if this is clinically justifiable. The decision whether to submit a patient whose VS increases in volume during follow-up to wait-and-scan, surgery, or repeat radiosurgery is of course always a clinical decision depending on many factors such as age, tumor size, neurological deficits, etc., and never just a matter of volume measurements.

Conclusions

Tumor progression or treatment failure needs to be differentiated from TTE. According to our data, time may be a good parameter distinguishing tumor progression due to tumor growth from TTE due to tumor swelling in VS following GKRS. A volume increase during the first 18 months of follow-up is most likely a transient phenomenon, which requires intervention only if the volume increase itself leads to neurological problems. A volume increase occurring during the first 3–4 years of follow-up or an ongoing volume increase past the first 3 years of follow-up is most likely indicative of tumor growth. As opposed to TTE, tumor growth is synonymous with treatment failure and therefore usually requires therapeutic action. If clinically justifiable, it may be prudent to postpone any additional intervention in the case of suspected tumor progression for at least 2 years or preferably 3–4 years following GKRS in order to avoid unnecessary surgery or repeat radiosurgery for TTE.

Conflicts of interest None.

References

1. Hasegawa T, Kida Y, Kato T, Iizuka H, Kuramitsu S, Yamamoto T (2013) Long-term safety and efficacy of stereotactic radiosurgery for vestibular schwannomas: evaluation of 440 patients more than 10 years after treatment with Gamma Knife surgery. J Neurosurg 118:557–565
2. Lomax NJ, Scheib SG (2003) Quantifying the degree of conformity in radiosurgery treatment planning. Int J Radiat Oncol Biol Phys 55: 1409–1419
3. Meijer OWM, Weijmans EJ, Knol DL, Slotman BJ, Barkhof F, Vandertop WP, Castelijns JA (2008) Tumor-volume changes after radiosurgery for vestibular schwannoma: implications for follow-up MR imaging protocol. Am J Neuroradiol 29:906–910
4. Mindermann T, Schlegel I (2013) Grading of vestibular schwannomas and corresponding tumor volumes: ramifications for radiosurgery. Acta Neurochir 155:71–74
5. Nagano O, Higuchi Y, Serizawa T, Ono J, Matsuda S, Yamakami I, Saeki N (2008) Transient expansion of vestibular schwannoma following stereotactic radiosurgery. J Neurosurg 109:811–816
6. Pollock B (2006) Management of vestibular schwannomas that enlarge after stereotactic radiosurgery: treatment recommendations based on a 15-year experience. Neurosurgery 58:241–248
7. Scheib SG, Gianolini S, Haller D, Wellis GN, Siegfried J (2000) VOLUMESERIES: a software tool for target volume follow-up studies with computerized tomography and magnetic resonance imaging. J Neurosurg 93(Suppl 3):203–207