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Linear accelerator radiosurgery for vestibular schwannoma: measuring tumor volume changes on serial three-dimensional spoiled gradient-echo magnetic resonance images

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Object. The authors report on a series of 46 patients harboring vestibular schwannomas (VSs) treated using linear accelerator (LINAC) radiosurgery and an analysis of serial magnetic resonance (MR) imaging data, specifically the changes in tumor volume.

Methods. Fifty-three consecutive patients underwent LINAC radiosurgery for VS between 1993 and 2002. Seven of these patients were lost to follow up. Three-dimensional (3D) spoiled gradient-echo (SPGR) MR imaging was performed at 3- to 4-month intervals after radiosurgery. Tumor volume was measured on Gd-enhanced MR images of each slice.

The median duration of follow-up MR imaging studies was 56.5 months (range 12–120 months). Follow-up imaging studies were conducted for longer than 1 year in 42 of 53 patients. Tumor volume changes were categorized into four types: enlargement (eight lesions [19%]), no change (two lesions [4.8%]), transient enlargement followed by shrinkage (19 lesions [45.2%]), and direct shrinkage (13 lesions [31%]). Two cases (4.8%) with twice the initial tumor volume required repeated radiosurgery. All cases of transient enlargement had subsequent shrinkage within 2 years after radiosurgery.

Nine (21.4%) of 42 patients demonstrated ventricular enlargement on MR images obtained after radiosurgery. Three patients (7.1%) required placement of a ventriculoperitoneal shunt because of symptomatic hydrocephalus, and another four cases (9.5%) spontaneously resolved.

Conclusions. Volume measurement on 3D-SPGR MR imaging was a suitable method to assess tumor changes. Volume changes beyond twofold or continuous enlargement for longer than 2 years after radiosurgery are key criteria in rating the effects of radiation. Some cases of hydrocephalus after radiosurgery resolved spontaneously and their rates of occurrence were similar to the typical incidence of hydrocephalus associated with VS.

KEY WORDS • vestibular schwannoma • tumor volume • linear accelerator radiosurgery • hydrocephalus • three-dimensional spoiled gradient-echo magnetic resonance imaging

VESTIBULAR schwannoma is a benign neoplasm arising from one of the vestibular nerves in the cerebellopontine angle and the internal acoustic meatus. Traditionally these tumors have been treated using resection or close observation. Stereotactic radiosurgery, introduced by Leksell[11] in 1951, has been offered to patients harboring these lesions as an alternative to surgical removal given its lower morbidity and tumor control that seems comparable to that achieved through resection.

The purposes of radiosurgery for VS include long-term prevention of tumor growth, maintenance of neurological function, and prevention of new neurological deficits throughout a patient's life. Note that tumor changes after radiosurgery raise concerns about the procedure's long-term efficacy. Follow-up imaging is needed to assess fully the effectiveness of lesion control. Currently, MR imaging is regarded as the most sensitive neuroimaging procedure to evaluate tumor response. Transient tumor growth and loss of central enhancement on images are generally accepted as characteristic changes in VSs following radiosurgery.[9,12,16,18,24,26,27]

To evaluate the effect of radiosurgery on VSs, it is very important to understand the behavior of these tumors following the application of radiation. Note that most descriptions in the literature involve experiences with gamma knife surgery; therefore, it would be useful to compare these data with those obtained using other radiotherapeutic modalities. In this paper, we report on our experience with the administration of LINAC radiosurgery in 46 patients harboring VSs. Moreover, we estimated the tumor volume change by using 3D-SPGR MR imaging. Although most authors[2,4,7,8,

Abbreviations used in this paper: CSF = cerebrospinal fluid; LINAC = linear accelerator; MR = magnetic resonance; SPGR = spoiled gradient-echo; VP = ventriculoperitoneal; VS = vestibular schwannoma; 3D = three-dimensional.

TABLE 1

Summary of patient characteristics before LINAC radiosurgery

Parameter	Value
no. of patients	46
male/female ratio	14:32
median age in yrs (range)	60 (21–78)
no. of previous resections (%)	12 (26.1)
median tumor vol in ml (range)	2.29 (0.4–7.01)
median duration of follow up in mos (range)	56.5 (12–120)

[10,15,20,21] have preformed conventional two-dimensional measurements, this method makes it difficult to delineate subtle tumor changes. To our knowledge, authors of cohort studies have not used volumetric assessment in determining the radiosurgical response, and thus our data may prove useful.[27]

Clinical Material and Methods

Patient and Tumor Characteristics

Between October 1993 and October 2002, VS had been diagnosed in 53 patients who underwent LINAC radiosurgery in our unit. Because seven of these patients were lost to follow up, data for analysis were obtained in 46 consecutive patients (14 men and 32 women) in this study (Table 1). The median age was 60 years (range 21–78 years). Twelve patients (26.1%) had previously undergone resection. All cases involved unilateral tumors with a median volume of 2.29 ml (range 0.4–7.01 ml).

Radiosurgical Procedure

In all patients, stereotactic radiosurgery was performed using a LINAC (Clinac 2100C; Varian Medical Systems, Milpitas, CA). A stereotactic headring was affixed to each patient's head following administration of a local anesthetic agent. Magnetic resonance images were obtained using thin slices (3 mm). Imaging data were transferred to a computer workstation running commercially available stereotactic treatment planning software (FL Fischer-Leibinger, Freiburg, Germany). Depending on the tumor size and configuration, one to four isocenters (median two isocenters) were targeted. The median radiation dose directed to the tumor margin was 14 Gy (range 10–16 Gy), and the median maximal dose was 23.2 Gy (range 17–36.13 Gy). Radiation applied to the brainstem was limited to 10 Gy.

Follow-Up Evaluations

All patients were followed up clinically and radiologically every 3 to 4 months through MR imaging, and the median duration of the follow-up MR imaging studies was 56.5 months (range 12–120 months). To measure tumor volume, we obtained 3D-SPGR MR imaging sequences using TR 45 msec, TE 3.1 msec, field of view 180 × 180 mm, slice thickness 1 mm, and matrix 256 × 160. Computer-assisted measurement calculated the tumor area in each Gd-enhanced MR image. Volume was determined by multiplying the area by section thickness. Tumor shrinkage or growth was defined as a volume change of more than 20%.

TABLE 2

Summary of characteristics in two cases subject to repeated treatment

Parameter	Case No. 1	Case No. 2
age (yrs), sex	52, F	44, F
1st radiosurgery		
tumor vol (ml)	1.69	0.59
marginal/max treatment dose (Gy)	14/17.42	14/19.62
2nd radiosurgery		
tumor vol (ml)	4.67	2.36
marginal/max treatment dose (Gy)	8/25	8/20.5
interval between treatments (mos)	29	36
tumor vol at last follow up (ml)	1.71	1.1

Results

Types of Tumor Volume Change

Among 46 patients, 42 were observed for more than 1 year through follow-up MR imaging studies. Tumor volume changes were categorized into the following four types. 1) Eight lesions (19%) showed enlargement (Fig. 1A). This type of volume change was further classified into two subgroups: persistent continuous enlargement and initial enlargement followed by a growth plateau. Three lesions demonstrated persistent continuous enlargement, and in two of these cases tumor volumes increased 2.76- and 3.99-fold (Table 2). Both of these tumors compressed the brainstem, and therefore the patients underwent radiosurgery again at 29 and 36 months after the first treatment and the lesions demonstrated acceptable shrinkage. The other five lesions displayed initial enlargement followed by a growth plateau. Radiation was not reapplied in this subgroup of patients because no warning symptom occurred during the short follow-up period. 2) Two lesions (4.8%) exhibited no change (Fig. 1B). 3) Nineteen lesions (45.2%) showed transient enlargement followed by shrinkage (Fig. 1C). Note that transient enlargement peaked at a median of 4 months (range 3–11 months) after radiosurgery. Nevertheless, this maximal enlargement did not reach twofold (that is, maximal enlargement 1.87-fold). Among these 19 cases, two schwannomas showed regrowth approximately 5 years after radiosurgery; therefore, the entire group was classified into two subgroups (transient enlargement followed by shrinkage and late regrowth). 4) Thirteen lesions (31%) demonstrated direct shrinkage (Fig. 1D). The minimal value of the reduction ratio was 0.05-fold (that is, from 5.5 to 0.25 ml) at 89 months after radiosurgery, which still represented continuous shrinkage.

Table 3 shows treatment characteristics for each type of tumor volume change. There was no significant difference in age, tumor volume, radiation treatment dose, and number of targeted isocenters among the four volume change categories.

Loss of Central Enhancement on Images of Tumors With Enlargement

The loss of central enhancement on MR imaging was recognized in 37 (88.1%) of 42 cases monitored longer than 1 year. The median duration of identification periods was

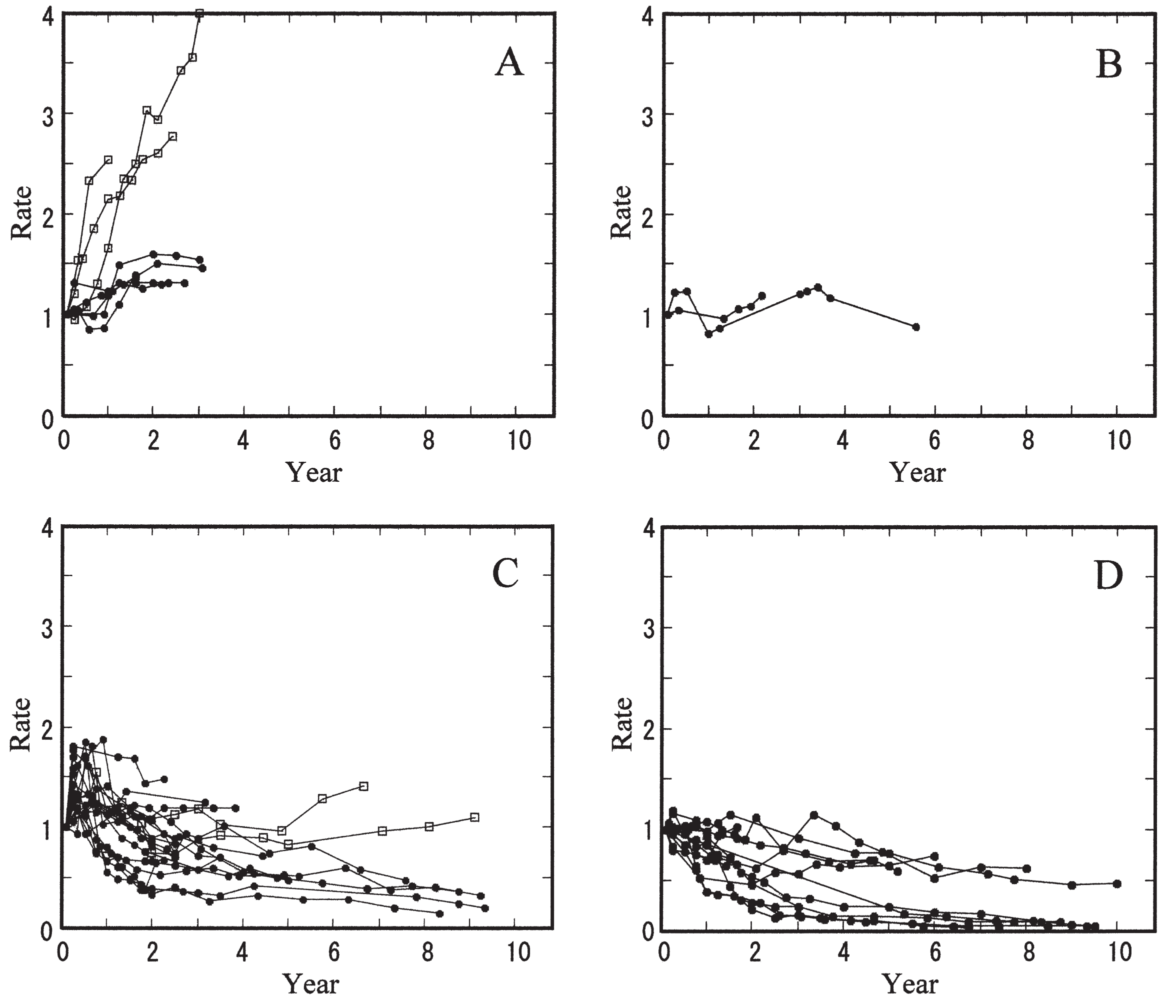

FIG. 1. Graphs depicting tumor volume change patterns in 42 patients more than 1 year after LINAC radiosurgery. A: Tumor enlargement (eight lesions). *Circles* represent initial enlargement followed by sustained tumor volume; *squares*, persistent continuous tumor enlargement. B: No volume change (two lesions). C: Transient tumor enlargement followed by shrinkage (19 lesions). *Circles* represent transient enlargement followed by tumor shrinkage; *squares*, late regrowth. D: Direct shrinkage (13 lesions). Rate refers to volume change rate, a comparison of volume before radiosurgery and that after radiosurgery. Year refers to that following radiosurgical treatment.

4 months (range 3–9 months). Twenty-two (59.4%) of these cases coincidentally had varied tumor enlargement patterns: 15 (68.2%) showed postradiation tumor shrinkage at a median interval of 3.5 months (range 1–9 months), and seven (31.8%) demonstrated increased tumor growth at a median of 4 months (range 3–12 months).

Hydrocephalus Associated With VSs

Four (7.5%) of 53 patients had symptomatic hydrocephalus on the initial visit. All of these cases were treated using a VP shunt and radiosurgery. One patient underwent CSF examination before radiosurgery. Protein content in the CSF was high (118 g/dl). Nine (21.4%) of the 42 patients monitored longer than 1 year demonstrated ventricular enlargement on MR imaging a median of 22.5 months (range 13–48 months) after radiosurgery. Three patients (7.1%) required the placement of a VP shunt because of symptomatic hydrocephalus. On the other hand, another four (9.5%) experienced spontaneous improvement within 1 year after the appearance of ventricular enlargement on MR images. Note that patients did not undergo CSF examinations during the follow-up period.

Tumor Control

In most cases, the tumor decreased in size over time. Favorable tumor control was documented in 31 (73.8%) of 42 patients in whom follow-up images had been obtained for longer than 1 year, 31 (81.6%) of 38 patients for longer than 2 years, and 18 (100%) of 18 patients for longer than 5 years. Eleven patients revealed a decrease in tumor size more than 7 years after radiosurgery, and 5 patients more than 9 years after radiosurgical therapy.

Two cases required repeated treatment, initial treatment having obviously failed. Overall, 95% of the series population did not have to undergo repeated treatment. On the other hand, two schwannomas showed late regrowth approximately 5 years after radiosurgery, although one lesion had increased 1.1-fold at the last follow up (109 months). That

TABLE 3
*Treatment characteristics according to type of tumor volume change**

Parameter	Volume Change Category 1	2	3	4
no. of patients	8	2	19	13
median age in yrs (range)	53.5 (39–78)	48 (29–67)	54 (21–74)	60 (40–76)
median tumor vol in ml (range)	2.155 (0.4–6.8)	1.69 (1.1–2.28)	1.965 (0.96–6.72)	2.61 (0.76–7.01)
median dose to tumor margin in Gy	14 (12–14)	14 (14)	14 (10–15)	14 (12–16)
median dose in Gy (range)	23.2 (17.42–31.2)	22.9 (20–25.8)	24.26 (17.5–36.13)	22.17 (17–30)
median no. of isocenters	2 (1–3)	1.5 (1–2)	2(1–4)	2(1–4)

* Tumor volume change categories: 1, volume enlargement; 2, no volume change; 3, transient volume enlargement followed by shrinkage; 4, direct volume shrinkage.

rate was 11.1% (two of 18 patients) among those followed up for longer than 5 years.

Procedural Complications

Data on hearing function were obtained in 37 patients. Before radiosurgery, 17 patients (46%) were considered to be totally deaf (Gardner–Robertson[6] Class V), nine (24.3%) to have useful hearing levels (Classes I and II), and 11 (29.7%) to have nonuseful hearing levels (Classes III and IV). Among the nine patients with useful hearing levels, six (66.7%) maintained useful hearing, including one patient who had suffered temporary deterioration. Overall, hearing was unchanged in 34 patients (91.9%) and deteriorated in three (8.1%). There were no improved cases in our series.

Nine patients exhibited facial palsy before radiosurgery, and only one patient experienced improvement in the palsy after radiosurgery. New facial palsy developed in two (4.8%) of 42 patients, and temporary facial palsy in one patient (2.4%). Trigeminal neuropathy occurred in four patients before radiosurgery, and symptoms were unchanged after treatment. New trigeminal neuropathy developed in one patient (2.4%).

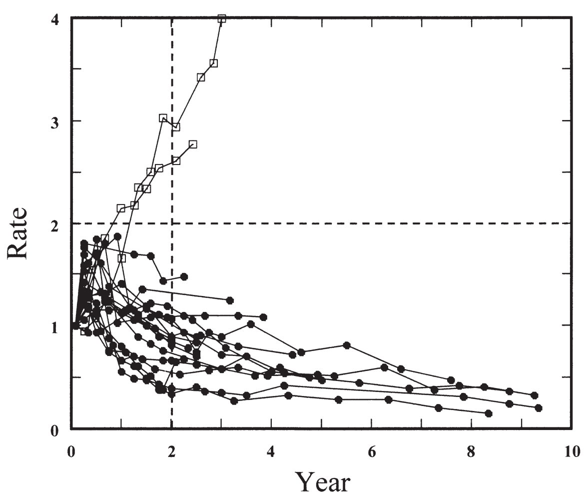

FIG. 2. Graph demonstrating tumor volume change in patients in whom follow-up images had been obtained for longer than 2 years (excluding the following subgroups: initial enlargement followed by sustained tumor volume and late regrowth). *Squares* represent continuous enlargement; *circles,* transient enlargement followed by shrinkage. Rate refers to volume change rate, a comparison of volume before radiosurgery and that after radiosurgery. Year refers to that following radiosurgical treatment.

Discussion

Radiosurgery has been used to treat patients with VSs for more than two decades. Many authors have reported good results.[2,4,7,8,10,12–15,20,21,25] As a whole, our data are comparable to those from other series, including the procedural complications.

In our series, tumor volume changes were categorized into four types. Nakamura, et al.,[16] grouped them into four different types: temporary tumor enlargement, no volume change/sustained regression, repeated alternate enlargement and regression, and continuous tumor enlargement. We did not recognize repeated alternate tumor enlargement and regression in our series, which was repeated alternating enlargement and regression of the tumor cystic component in their series. On the other hand, Yu, et al.,[27] categorized three tumor change types by volume mapping (Leksell GammaPlan software; Elekta Instruments, Norcross, GA): transient swelling followed by shrinkage, direct shrinkage, and continuous enlargement. Based on accurate volume measurements, these authors described no case of stable tumor volumes. In contrast, we recognized instances of no-volume change (only two cases), although the tumor size was estimated using similar volume measurement procedures. Thus the definition of "volume change" affected whether the no-volume change type was recognized. Recently, transient enlargement after radiosurgery has been a widely recognized phenomenon.[9,12,16,18,24,26,27] It is important to distinguish between transient enlargement and continuous enlargement when radiation effects are evaluated during the follow-up period.

In the present series, no transient enlargement more than twice the initial tumor volume was observed. Two cases with twice the initial tumor volume needed repeated treatment because of continuous tumor growth and brainstem compression. Moreover, all transient enlargements were followed by shrinkage within 2 years after radiosurgery. These results indicated that a twofold increase or a continuous enlargement during more than 2 years is a key criterion in rating the effects of radiation (Fig. 2). In the current series, eight lesions (19%) showed enlargement, which was classified into two subgroups. Two cases of persistent continuous tumor enlargement were treated again with radiosurgery and a third had too short a follow-up period (19 months) to determine the radiation effects. Five patients with a sustained tumor volume after an initial growth period required no repeated treatment presently. Note that some patients in this volume subgroup might experience late tumor shrinkage in a few years. It is impossible to distinguish such a response as treatment failure or prolonged swelling; therefore, a longer follow up is imperative.

Some authors have shown that the loss of central enhancement on MR images commonly occurs with transient tumor growth.[9,12,16,18,24,26,27] In the present series, central enhancement loss was demonstrated on images obtained in 37 patients (88.1%), of which 22 patients (59.5%) coincidentally varied with enlargement. These high rates of central enhancement loss concurrent with tumor enlargement might be a result of close neuroimaging follow-up and volume measurement. These findings not only support previous data,[9,12,16,18,24,26,27] but also indicate that the loss of central enhancement with tumor growth is a more common phenomenon after radiosurgery.

Regarding volume change after central enhancement loss concurrent with tumor growth, 15 of 22 cases of tumor growth were followed by shrinkage, and seven by additional growth. The period from central enhancement loss to additional tumor growth was a median of 4 months, a time slightly longer than that in cases of subsequent shrinkage (3.5 months). This finding and the high rate of central enhancement loss indicate a radiation effect, although tumor proliferation will be superior to the radiation effect in cases followed by additional tumor growth. Note, however, that authors of previous studies[2,16] have described no significant correlation between central enhancement loss and tumor shrinkage.

Although an association between hydrocephalus and VSs is well recognized,[19,23] the frequency and mechanisms are not well established. In the present series, ventricular enlargement was observed on MR images in nine cases (21.4%) 7 to 38 months after radiosurgery. Furthermore, symptomatic hydrocephalus requiring a VP shunt 13 to 44 months after radiosurgery occurred in three cases (7.1%). Reportedly, 3.7 to 15% of patients with cerebellopontine angle tumors suffer from hydrocephalus,[1,3,12,14,19,21] and 3 to 12% after radiosurgery.[5,7,10,13,15,17,21,22,24] The incidence of hydrocephalus in our series was similar to that in previous reports. Although Sawamura, et al.,[21] reported on cases of symptomatic hydrocephalus within 2 years after fractionated stereotactic radiosurgery, the disease occurred 44 months after radiosurgery in one of our cases. Note, however, that another four cases (9.5%) spontaneously improved within 1 year after the appearance of ventricular enlargement. The pathophysiological mechanism is generally believed to be CSF malabsorption due to elevated protein levels from tumor cells as a result of radiation-induced necrosis.[17,19] Although we did not conduct CSF examinations, we think that hydrocephalus associated with VS is caused by an elevation in CSF protein levels. In the spontaneously improved cases, perhaps the protein leakage stopped before symptomatic hydrocephalus developed.

Pirouzmand, et al.,[19] described some cases of resolved hydrocephalus following tumor resection. Data from cases in the present study revealed that hydrocephalus after radiosurgery also resolved and that radiosurgery did not always increase the risk of secondary hydrocephalus associated with VSs.

In the present study, another characteristic finding was the regression of some VSs for a significantly long period after radiosurgery. Tumor volume decreased in seven patients more than 7 years after radiosurgery, and in two patients more than 9 years postradiosurgery. These results indicated that radiosurgery has long-term effects, at least for VSs. On the other hand, two lesions showed regrowth approximately 5 years after radiosurgery. They were thought to be recurrent cases that needed close observation. From these findings, we speculated that tumor volume change in VSs was associated with the balance of radiation effects and tumor activities.

Conclusions

Radiosurgery is becoming an increasingly attractive alternative to microsurgery in the treatment of VSs. Our results using LINAC radiosurgery showed good tumor control rates in line with those in previous reports. Some cases of hydrocephalus following radiosurgery spontaneously resolved, and this procedure did not increase the risk of secondary hydrocephalus associated with VSs, whose rates were similar to the natural rates of hydrocephalus associated with these lesions. Serial 3D-SPGR MR images of VSs after radiosurgery were useful to assess tumor changes and to measure lesion volume. Tumors characterized by transient growth showed subsequent shrinkage within 2 years after radiosurgery, with a less than twofold volume change. We propose that a twofold increase or continuous increases in tumor volume for more than 2 years is one of the key criteria in rating the effects of radiation.

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