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Original Article

Long-term outcome of Gamma Knife radiosurgery in patients with tiny intracanalicular vestibular schwannomas detected by three-dimensional fast imaging employing steady-state acquisition magnetic resonance

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ABSTRACT

Objective: To evaluate the effectiveness and long-term outcome of Gamma Knife radiosurgery (GKRS) for tiny vestibular schwannomas (VSs) detected by three-dimensional fast imaging employing steady-state acquisition magnetic resonance (3D-FIESTA MR).

Materials and methods: Between January and December 2004, 3D-FIESTA MR of the brain was performed in patients who had physical health examinations at the Buddhist Tzu Chi General Hospital (Hualien, Taiwan). Tiny intracanalicular VSs (defined as a tumor volume < 0.5 cm^2) was detected in 13 patients (8 women and 5 men). The mean age of the patients was 60 years (range, 45–84 years). Hearing function was graded using the Gardner–Robertson (GR) classification. Dose planning was performed on intra-operative stereotactic contrast-enhanced images using multiple 4-mm isocenters. The mean tumor volume was 0.098 cm^2 (range, 0.013–0.4 cm^2). The mean margin dose was 12.4 Gy (range, 11–14 Gy), and the isodose line was set at a mean of 53.8% (range, 50–70%).

Results: Twelve patients had GR Grade I or II hearing before GKRS, and GR I or II hearing was maintained in 11 patients. Facial and trigeminal nerve functions were preserved in all patients. The tumor control rate was 100% at a mean follow-up period of 9.8 ± 1.1 years (range, 76–126 months). One patient developed acute vertigo 1 day after GKRS, which subsided after short-term use of steroids and did not recur.

Conclusion: With the application of 3D-FIESTA, tiny VSs can be detected early. Because low-dose (12–14 Gy) GKRS is safe and effective for long-term control of the growth of tumors with acceptable preservation rate of hearing function, it may be worthwhile to use 3D-FIESTA to detect tiny VSs and treat the patients using GKRS.

1. Introduction

Vestibular schwannomas (VSs) represent approximately 10% of all primary brain tumors, with an estimated annual incidence of one case per 100,000 individuals [1,2]. A European report showed that the number of VSs diagnosed each year has increased threefold in recent decades from the era of radiography to the era of computed tomography and magnetic resonance imaging (MRI). Over the same period, the mean size of the tumor at the time of diagnosis has gradually decreased from 35 (extrameatal diameter) to 10 mm [3–5]. Similar changes in the incidence and size have been reported in other studies [4–6]. With the decrease in tumor size at diagnosis, there are fewer symptoms, and unilateral sensorineural hearing reduction may be the only symptom [6–8].

Conflicts of interest: none.

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Recently, with advances in current MRI techniques, such as three-dimensional fast imaging employing steady-state acquisition magnetic resonance (3D-FIESTA MR), the chances of finding asymptomatic patients with tiny VSs have improved. Using the 3D-FIESTA technique, the anatomic structures within the internal acoustic canal (IAC) can be clearly visualized without gadolinium enhancement [9]. Therefore, there has been an increase in incidental visualization of intracanalicular VSs without significant symptoms and signs (Fig. 1). This raises a question about whether these tumors in the acoustic canal should be treated.

Gamma Knife radiosurgery (GKRS) was first performed by Leksell in 1969 [10]. Over the years, with advanced dose-planning software, MRI-guided dose planning, and dose optimization, the evolution of radiosurgery has revolutionized the management of VSs [11]. During the last decade, radiosurgery has emerged as an effective alternative to surgical removal of small- and moderate-sized VSs. To date, the concepts of performing radiosurgery for VSs have focused on the control of tumor growth, preservation of hearing function, and prevention of other cranial neuropathy with the application of low-dose radiosurgery [12–21].

This article seeks to delineate the long-term outcome of GKRS for proactive treatment of tiny intracanalicular VSs detected by 3D-FIESTA MR.

2. Materials and methods

2.1. 3D-FIESTA MR study

Between January and December 2004, 3D-FIESTA MR studies were performed on patients who received physical health examinations. The 3D-FIESTA pulse sequence provides excellent high-resolution images of fluid-filled structures with very short acquisition times. The FIESTA technique employs ultrashort repetition times and echo times, with very fast scan times and outstanding image contrast. This bright fluid sequence uses steady-state contrast mechanisms to provide high signal-to-noise ratio images with a strong signal from fluid while effectively suppressing background tissue. With the application of 3D-FIESTA MR, those anatomic structures within the acoustic canal can be better delineated, and contrast medium is not needed at the primary survey. Because gadolinium-enhanced MRI remains the gold standard for the detection of VSs, contrast study could be reserved for those patients with tumors shown on 3D-FIESTA MR (Fig. 2).

Unilateral tiny VSs (defined as a tumor volume < 0.5 cm^2) were detected in 13 patients with this procedure. The clinical characteristics of these patients are listed in Table 1. The patient series consisted of eight women and five men. The median age of patients was 60 years (range, 45–84 years). Audiograms for hearing function tests on the lesion side were evaluated according to the Gardner–Robertson (GR) classification [22]. Twelve patients had serviceable hearing function on the lesion side ear before treatment (defined as GR Class I and II), and one patient had Class III hearing function. Eight patients experienced minor symptoms such as tinnitus, vertigo, headache, or a combination of these symptoms. One patient had a family history of neurofibromatosis (type II), and his unilateral VS was found in a family survey by 3D-FIESTA study. Neither trigeminal nor facial neuropathy could be detected before treatment in any of the 13 patients. The tumor volume varied from 0.013 to 0.4 cm^2.

2.2. Radiosurgery technique

The procedure began with rigid fixation of a Leksell stereotactic frame (Model C; Elekta Instruments, Stockholm, Sweden) to the patient's head. Local anesthesia was applied to the scalp (5% bupivacaine and 2% lidocaine). MR stereotactic images were acquired with a fiducial system attached to the stereotactic frame and transported through a fiber optic Ethernet cable to the GammaPlan (Elekta Instruments) computer, in which images were checked for distortion/accuracy. Planning was performed on 1- or 2-mm slice thickness axial MR images with coronal and sagittal reconstructions. After optimizing the plan, a maximum dose to the target was determined. Radiosurgery was performed with a 201-source, cobalt-60 Gamma Knife and the patients' heads and stereotactic frames were immobilized within the appropriate collimator helmet at a calculated target coordinate. The treatment was accomplished in a single session by positioning the head serially for each subsequent isocenter until a fully conformal field encompassed the tumor volume.

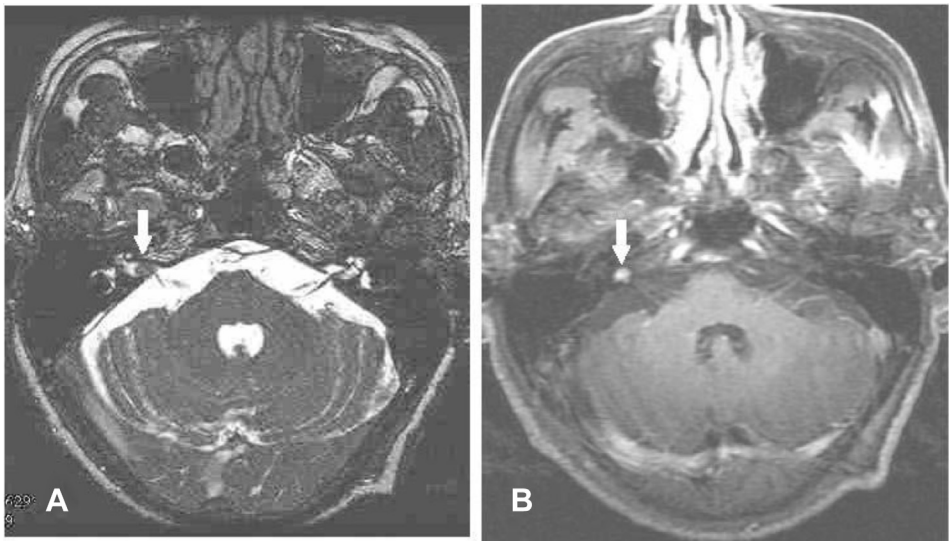

Fig. 1. (A) Three-dimensional fast imaging employing steady-state acquisition magnetic resonance shows an intracanalicular vestibular schwannoma (VS, white arrow) in the right internal acoustic canal. (B) Contrast magnetic resonance-enhanced study confirms the tiny VS (white arrow).

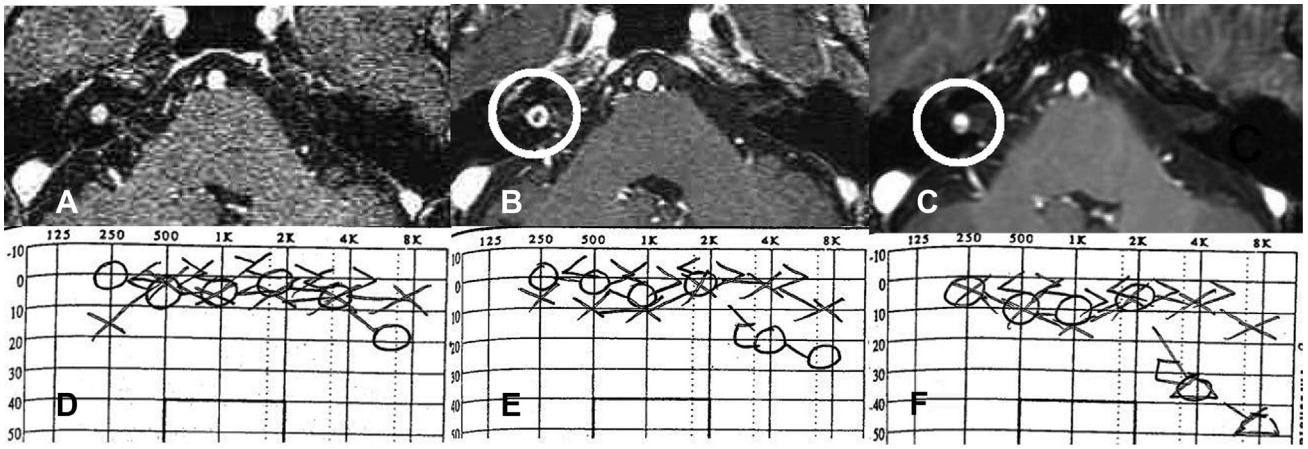

Fig. 2. Serial magnetic resonance imaging (MRI) of a 55-year-old man with a tiny vestibular schwannoma (VS). (A) Axial MRI at the time of Gamma Knife radiosurgery (GKRS) demonstrating a tiny VS in the right internal acoustic canal. (B) Follow-up MRI shows central hypointensity in the tiny VS (circle) 6 months after GKRS. (C) Follow-up MRI 3 years and 4 months after GKRS shows normalization of the tiny VS without enlargement, and the central hypointensity has disappeared. The comparable pure tone audiogram checked around the time of the aforementioned MRI studies showed no significant changes in 500–4k but a decline in some high-pitched sounds. Images (D), (E), and (F) correspond with images (A), (B), and (C), respectively.

2.3. Imaging for tiny VS radiosurgery

Three-dimensional volume-acquisition MRI was performed using a spoiled gradient recalled acquisition in steady-state pulse sequence (divided into 40–60 slices, 1- or 2-mm thickness) to cover the entire lesion surrounding the critical structures.

2.4. Radiosurgical dose planning

A conformal plan was created using GammaPlan Software (Elekta Instruments). Because the tumors were small, the smallest beam diameters were used. Only 4-mm collimators were used to irradiate the intracanalicular tiny VSs in this study. As the facial and the acoustic nerve complex usually coursed along the anterior margin of the tumor, the dose plan was highly conformal in this area. The tumor margin doses were 11 ($n = 1$), 12 ($n = 7$), 13 ($n = 4$), and 14 Gy ($n = 1$) and the median margin dose was 12 Gy. The maximum dose ranged from 16 to 26 Gy (median, 24 Gy). The marginal tumor dose was prescribed to the 50% isodose line in eight patients, 55% in three, 60% in one, and 75% in one. The number of isocenters used for each patient varied from one to 10 (median, 4).

Table 1
Clinical characteristics of 13 tiny vestibular schwannoma patients.

Characteristics	Values
No. of patients	13
Age (y)	60.9 ± 10.0 (45–84)
Sex (M:F)	5:8
Tumor volume (cm^3)	0.098 ± 0.118 (0.013–0.400)
Minor symptoms[a]	12
Pre-GK hearing status	
GR Grade I	10
GR Grade II	2
GR Grade III	1
Prescription dose (Gy)	12.4 ± 0.8 (11–14)
Isodose line percentage	53.8 ± 7.1 (50–75)
No. of shots	4.4 ± 2.7 (1–10)
Treatment with plug shielding	4
Follow-up period (mo)	118 ± 13 (76–126)

F = female; GR = Gardner–Robertson grade; M = male; pre-GK = pre-Gamma Knife radiosurgery.
[a] Minor symptoms include balance problems, tinnitus, vertigo, dizziness, or headache.

In four patients, the plugging method was adopted for shaping the isodose line to achieve higher conformality.

2.5. Postoperative care and evaluation

All patients received an intravenous dose of betamethasone (8 mg) at the end of the procedure. The stereotactic frame was removed immediately after radiosurgery. The patients were observed in the ward and were discharged 1 day after treatment. After radiosurgery, all patients were followed with serial gadolinium-enhanced MRI, at around 6 and 18 months post-GKRS, and then every year subsequently. All patients who had preserved hearing were advised to undergo audiologic evaluation such as a pure tone audiogram and speech discrimination study during an MR follow up. Audiological data were compared with our pre-treatment baseline data. Preradiosurgery and postradiosurgery hearing were graded using the modified GR classification [22]. In addition, preradiosurgery and postradiosurgery facial and trigeminal nerve functions were also assessed in all patients, and the facial nerve functions were classified according to the House–Brackmann grading system [23]. The duration of follow up in this series varied from 76 to 126 months (median, 118 months).

3. Results

3.1. Tumor growth control

Radiographic tumor progression was strictly defined as any temporary or sustained increase in the tumor diameter by at least 1 mm in two dimensions or 2 mm in any direction. The median follow-up period was 118 months (range, 76–126 months). Loss of central contrast uptake with minimal temporary tumor enlargement was noted in four patients, but these tumors were the same size as or smaller than the original tumors 1 or 2 years later. There was neither any change nor decrease in the tumor size on long-term follow up after GKRS. The clinical and radiological tumor control rate was 100%.

3.2. Hearing preservation

Audiological data are presented in Table 2. Immediately after radiosurgery, all patients (100%) maintained their preoperative

Table 2
Hearing classification in 13 patients with vestibular schwannomas.

Class description	Pure tone average (dB)	Speech discrimination score (%)	Number of tumors	
			Pre-GK	Post-GK
I	0–30	70–100	10	9
II	31–50	50–69	2	2
III	51–90	5–49	1	2
IV	91 to maximum	1–4	0	0
V	None detectable	0	0	0

GK = Gamma Knife radiosurgery.

level of hearing. During follow up, hearing levels (GR hearing class) were maintained and preserved in 11 of 12 patients with Grade I to II hearing levels.

3.3. Facial and trigeminal nerve functions

All 13 patients who had Grade I facial function before the surgery preserved their function after radiosurgery. No patient developed trigeminal neuropathy.

3.4. Functional outcome

All patients were discharged 1 day after radiosurgery and returned to their normal activities. No patient had a change in employment status because of this disease and treatment during the follow up; in addition, none of the patients in this series required additional surgery for the tumor by the time of the last follow up. Only one patient had adverse radiation effects with acute exacerbation of dizziness and vertigo for 5 days after radiosurgery. However, these symptoms improved after treatment with steroids and did not recur during the follow-up period.

4. Discussion

4.1. Treatment modality

The treatment options offered to patients with VSs have changed. About three decades ago, treatment was limited to microsurgery. Microsurgery was considered the standard approach for treatment of VSs, especially for large tumors compressing the brain stem in patients with balance disability. With small tumors or intracanalicular VSs, the options included a wait-and-see policy, microsurgery, and stereotactic radiosurgery. In microsurgery, concerns stem from the potential morbidities associated with intracranial procedures. Both tumor size and the surgeon's experience are risk factors [24]. Hearing loss is an obvious morbidity, and deafness reportedly occurs in 50% of patients [25]. Preservation of hearing has been reported at very low rates in patients with tumors greater than 2 cm [24]. A meta-analysis of the literature from the 1990s identified other complications in 21.9% of cases [26]. The mortality rate was very low (0.3%) and cerebrospinal fluid (CSF) leak was the most common morbidity (10.95%). Other complications were facial nerve transection (3.9%), meningitis (1.2%), and damage to other cranial nerves (1.1%). Another review of the literature reported mortality in 0–2% of patients, CSF leakage in 3–15%, facial nerve transection in 2.5–7%, and meningitis in 1–3% [24]. Data on minor symptoms such as tinnitus, vertigo, and balance have rarely been reported. Régis et al [20] used objective results and questionnaires to compare the results of radiosurgery with microsurgery. The results indicated no new facial weakness in 100% of patients who underwent GKRS compared with 63% of patients who underwent microsurgery. Ninety-one percent of patients treated with GKRS (61% for microsurgery) had no functional deterioration after treatment. The mean hospital stay was 3 days after GKRS and 23 days after microsurgery. All working patients who underwent GKRS continued the same professional activities, compared with 56% in the microsurgery arm. The mean time away from work was 7 days for the GKRS group compared with 130 days for patients in the microsurgery group. Seventy percent of patients with a Class I preoperative hearing level (GR scale) had preserved functional hearing after GKRS (Class I and Class II) compared with only 37.5% in the microsurgery group. Findings after 4 years' follow up indicated that GKRS provided better functional outcomes than microsurgery. In our series, only one patient developed reduction of the hearing from Grade II to III; all other patients with Grade I hearing showed good preservation of hearing function. Patients with IAC tumors usually have no significant clinical symptoms and signs. These patients might desire a less invasive intervention than microsurgery, such as a wait-and-see policy or GKRS, which usually does not require general anesthesia or opening of the skull.

4.2. Radiosurgical tumor control and dosage

The ultimate goal of radiosurgery in VSs is control of tumor growth. Recent reports suggest an encouraging tumor control rate of 93–100% after performing radiosurgery for VSs [15,17,21,27,28]. Kondziolka et al [15] studied the 5–10-year outcomes in 162 patients with acoustic tumors who underwent radiosurgery at the University of Pittsburgh. In that study, a long-term tumor control rate of 98% was reported; 62% of tumors became smaller, 33% remained unchanged, and 6% became slightly larger. Some tumors initially enlarged 1–2 mm during the first 6–12 months after radiosurgery as they lost their central contrast enhancement. In our study, four patients had a similar response after radiosurgery. These tumors invariably regressed in volume compared with their pre-radiosurgical size. Only 2% of patients in that study underwent tumor resection after radiosurgery. Niranjan et al [17] analyzed the outcome of intracanalicular acoustic tumor radiosurgery performed at the University of Pittsburgh. All patients (100%) had imaging-documented tumor growth control. Flickinger et al [28] performed an outcome analysis of VSs patients treated between August 1992 and August 1997 at the University of Pittsburgh. Radiosurgery was performed as the primary treatment in 192 patients. The actual 5-year clinical tumor control rate (no requirement for surgical intervention) was 99.4% ± 0.6%.

The dose prescription for VSs has also changed significantly over the last 15 years. Initially, the dose delivered to the tumor margin (i.e., 18–20 Gy) was based on experience in a Swedish study [29]. However, the dose to the tumor margin was decreased to an average of 16–18 Gy within the first 2 years and by 1992, it was decreased further to 14–16 Gy [15]. Gradual reduction in doses has improved hearing preservation rates and reduced facial and trigeminal neuropathies. For the last 10 years, 13 Gy has been selected as the usual tumor margin dose [12]. This dose has been associated with a low complication rate while maintaining a high rate of tumor control.

The goals of VSs radiosurgery have evolved and there is much more emphasis on the maintenance of neurological functions and prevention of new neurological deficits along with long-term prevention of tumor growth. In 1996, Flickinger et al [30] defined the relationships between dose and tumor diameter for the risks of developing trigeminal, facial, and acoustic neuropathies after performing radiosurgery for VSs. The development of postradiosurgery neuropathies affecting cranial nerves V, VII, and VIII was correlated with a minimum tumor dose and transverse tumor diameter [30]. This result might suggest that there would be lower complication rates after radiosurgery if those VSs are treated as early as possible. In our series, we used the 3D-FIESTA to detect IAC VSs, and

proactively treated patients with a low dosage. In the 10-year follow up, a tumor control rate of 100% and a low rate of hearing reduction were noted. We preserved serviceable GR hearing levels in 11 of the 12 patients treated in this study. This finding seems compatible with the results reported by Flickinger and co-workers.

4.3. Wait-and-see policy

For patients with small or medium intracanalicular VSs, one of the alternatives is a wait-and-see policy. Most patients with small tumors do not have a rapidly progressive neurological syndrome yet some have persistent hearing loss, tinnitus, vertigo, headache, or a combination of these symptoms. These symptoms do not improve consistently after resection or radiosurgery [31]. Therefore, many patients now prefer a policy with minimal risk.

One pathological study postulated that IAC tumors might belong to a distinct category of VSs. Martin et al [32] reported on 144 VSs and showed that 100% of IAC VSs displayed Antoni type A architecture, whereas the large tumors had a B-type pattern (76.8%). This might indicate that IAC VSs are less aggressive and most are stable in the long term. Therefore, many researchers recommend sequential follow up for small IAC tumors with increased attention to changes in tumor volume and hearing function. However, untreated tumors in the brain did grow in a proportion of patients.

Suryanarayanan et al [33] assessed the outcome of conservative management in 436 patients with VSs in an observational study. One third of tumors did grow during a mean follow up of 3.6 years. The authors, however, did not recommend conservative management for sporadic tumors with an intracranial diameter of 1.5 cm or more. In growing tumors, the mean growth rate was 1.1 mm/year for sporadic tumors and 1.7 mm/year for neurofibromatosis type II tumors. Similar results were reported with a wait-and-see policy in other reviews of VSs behavior [25,33–36]. In our study, the tumors did not grow during long-term follow up after low-dose GKRS, although transient tumor enlargement with central hypointensity was found in four cases. However, can a wait-and-see policy be more beneficial for patients with IAC VSs? Can a small tumor grow and functional hearing change during observation or remain unchanged for the patient's entire life span? Régis et al [37] compared a wait-and-see policy and proactive GKRS in small IAC VSs. Forty-seven patients with intracanalicular VSs were followed prospectively along with a control group of 34 patients with unilateral intracanalicular VSs who were consecutively treated by GKRS and had functional hearing at the time of radiosurgery. Treatment failure was defined as tumor growth requiring treatment. In the wait-and-see group, treatment failure was observed in 35 patients (74%) but in the control (GKRS) group, it occurred in only one (3%) of the 34 patients. In the wait-and-see group, 60% of patients demonstrated no change of GR hearing class. Fifteen patients (38%) experienced more than 10 dB of hearing loss and two of them became deaf. At 3, 4, and 5 years, the useful hearing preservation rates were 75%, 52%, and 41% in the wait-and-see group, but 77%, 70%, and 64% in the GKRS control group, respectively. Thus, the chances of maintaining functional hearing and avoiding further intervention were much higher in cases treated by GKRS (79% and 60% at 2 and 5 years, respectively) than in cases managed by the wait-and-see strategy (43% and 14% at 2 and 5 years, respectively).

There is still no consensus regarding the selection of candidates for therapeutic intervention because the growth rate of VSs is unpredictable [38]. However, a management strategy that maintains cranial nerve functions, reduces treatment-associated morbidity, and allows the patient to resume a normal lifestyle as quickly as possible after intervention is desirable [31]. Many patients, especially those with minor symptoms and tiny VSs, which are detected early, might prefer radiosurgery to surgical resection because of the lower morbidity and similar rates of long-term tumor control with this procedure. Our series showed good preservation of cranial nerve functions as well as the good control of tumor growth over 10 years. We posit that the proactive treatment of tiny IAC VSs is desirable.

In conclusion, with the application of 3D-FIESTA, tiny VSs can be detected early. The low irradiation dose (12–14 Gy) for GKRS has been proven effective for long-term control of tumors with good preservation of neurological functions. It may be worthwhile to use 3D-FIESTA to detect tiny VSs and treat those tumors with low-dose GKRS.

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