INTRODUCTION

Vestibular schwannoma (VS), an intracranial extra-axial tumor, is originated from the Schwann cell sheath of either vestibular or cochlear nerve of the eighth cranial nerve. VS comprises about 80% of the cerebellopontine angle tumors and 6–8% of all intracranial tumors. Approximately 65–75% of tumors stem from the inferior branch of the vestibular nerve of the eighth cranial nerve. 

[14,15]
Treatment options of VS include surgical removal of the tumor, controlling tumor growth by stereotactic radiotherapy or radiosurgery, and careful serial observation. Surgical total resection remains the choice of tumor eradication. Despite significant advances and innovations in microsurgery technique, microsurgical excision of VS had many severe complications such as disequilibrium, lower cranial nerve palsies, cerebrospinal fluid leakage, and facial nerve palsy.[18,21,23] In contrast, stereotactic radiosurgery (SRS, Gamma Knife®, Cyberknife®) hails tumor growth using radiation delivered maximally to target tissues while minimizing adjacent exposure to the normal brain. The previous studies have proved Gamma Knife’s efficacy and safety in treating VS.[8,11,16,20,22,26,29] In the most recent report, compared with classical Gamma Knife, the rotating gamma system had less spontaneous coil movements, higher precision of the isocenter location, more beam stability, and less scattered radiation to the patient. Therefore, the RGK had advantages in the treatment of skull base tumors. However, more data on the long-term efficacy and safety of RGK in the management of VS is warranted. This study aims to evaluate the long-term neurological outcomes of RGK for VS in Vietnam.

MATERIALS AND METHODS

Study design

This was a prospective longitudinal single-center study. From October 2011 to October 2015, 89 patients with VSs were treated by RGK. The follow-ups lasted until June 2017. These cases were selected consecutively. This study was conducted at the nuclear medicine and Oncology Center, Bach Mai Hospital, Bach Mai Hospital, a tertiary referral hospital, was established in 1911 by the French and is considered one of Vietnam’s largest hospitals. This is an academic and community hospital.

According to our institutional practices, RGK was recommended as the primary treatment for minimally symptomatic VSs measuring <2.2 cm in maximal diameter. In contrast, microsurgical resection was recommended as first-line therapy for patients presenting with debilitating pre-treatment symptoms, larger tumors with maximal diameter >3 cm or mass effect on surrounding structures.[10,16,28] In the case of symptomatic tumors measuring from 2.2 cm to 3 cm, RGK was considered for patients with severe comorbidities, high-risk surgery, and who denied surgery. The final treatment decision was made based on a thorough pre-treatment consultation with patients. We included in our study 89 consecutive patients fulfilling the following inclusion criteria: all patients with VS received RGK as the protocol mentioned above. VSs consisted of newly diagnosed, postoperative residual, and recurrent tumors. Patients affected by neurofibromatosis type 2 were excluded from the study. On magnetic resonance imaging (MRI), the VS features were an intracranial extra-axial tumor of the cerebellopontine angle, which had an intracanalicular component, and widened the porus acusticus. This tumor was demarcated with adjacent tissues and showed avid homogenous or heterogeneous contrast enhancement.

Our Institutional Review Board approved the experimental protocol as well as the informed consent for this study. All patients with VS were consulted by interdisciplinary healthcare professionals, including neurosurgeons, neurologists, radiologists, radiation oncologists, pathologists, and otolaryngologists. The consensus treatment plan was discussed with the patients and their family members.

On the treatment day, after being administered a local anesthetic for immobilization, the patients underwent the application of a stereotactic head frame. Pre-treatment volumetric MRI sequences included 1-mm, axial, T1-weighted, contrast-enhanced images, 1–1.5-mm, axial, T2-weighted volume images, and 3-mm, T2, whole-head imaging. The SRS scenario was planned by the software. Based on the tumor’s contour, site, and size, the different shots (18 mm, 14 mm, 8 mm, and 4 mm) were designed to aim that the 50% isodose line circumscribed the tumor. The 40%, 30%, and 20% isodose lines were evaluated. The dose-volume histograms (DVH) were used to assess the SRS plans. Stereotactic radiosurgery was performed using the Rotating Gamma System Gamma ART-6000™ (American radiosurgery Inc., San Diego, CA, USA). The prescribed SRS dose was 10–16 Gy to the 50% isodose line. The doses for brain stem, cranial nerves (V, VII, and VIII), and cochlea were generally kept below 14 Gy, 12 Gy, and 4 Gy, respectively. Radiation delivery to the brainstem was estimated in a dose-volume fashion (DVH-based). We planned to keep 12 Gy-volume (V12) = 0 and V10 <1 cc to avoid possible issues with focal radionecrosis. In the case of postoperative residual and recurrent tumors, we had difficulty determining cranial nerves (V, VII, and VIII) on MRI. Therefore, empirically estimated doses for these cranial nerves were calculated based on multidisciplinary discussions which included neurosurgeons, radiologists, and radiation oncologists. Post-treatment follow-up assessments were performed at 3, 6, 12, 24, and 36 months. The work has been reported in line with the PROCESS criteria.[1]
Statistical analysis

The patients were assessed clinically and radiologically. Primary outcomes were radiological tumor control rate, hearing function, vestibular function, facial nerve palsy, and trigeminal neuralgia. Hearing function was evaluated by Gardner-Robertson classification. Facial nerve deficit was clinically assessed using the House-Brackmann index before and after treatment. Different symptomatic outcomes analyzed included lateralized headache, tinnitus, vertigo/dizziness/disequilibrium, trigeminal neuralgia, and secondary malignancies. Radiographic tumor control was defined based on the time from gamma knife radiosurgery (GKRS) until the development of either asymptomatic or symptomatic radiographic progression. Radiographic progression was defined as persistently increased maximal tumor diameter by at least 2 mm than the last MRI within at least 6 months. Trigeminal neuropathy was defined as new facial numbness or trigeminal neuralgia as reported in the patient chart. It was recorded as either present or absent. The rate of new trigeminal neuropathy was calculated as the percentage of patients with trigeminal neuropathy at follow-up. Vestibular nerve dysfunction was assessed by the presence or absence of balance difficulty before and after treatment. The vestibular nerve dysfunction was new if it was reported after but not before GKRS, and it was written as worse if the patient record explicitly stated that the functioning was worse after GKRS.

Data analysis was performed using STATA® version 14.0 (StataCorp., Lakeway Drive College Station, Texas, USA). Statistical significance was set arbitrarily at \( P < 0.05 \). The quantitative variables were presented as mean ± standard deviation if the data were normal distribution and were shown as the median and interquartile range if the data were non-normal distribution. The qualitative variables were presented as frequency and proportions. We used the Wilcoxon signed-rank test to compare the difference between the two paired groups. Kaplan-Meier estimator evaluated radiological progression-free survival.

Ethical considerations

The Institutional Review Board at Nuclear Medicine and Oncology Center of Bach Mai Hospital and Hanoi Medical University, Hanoi, Vietnam, approved data collection, analysis, and publication of this study. The study was performed within ethical standards. All potential participants were given information on the study’s purpose, the associated risks, and benefits and were required to provide written informed consent before inclusion in the study. Parents or legal guardians provided written consent for participants aged <18 years.

RESULTS

Participants and descriptive data

A total of 89 patients with VS were treated by RGK. Thirty-one patients were lost to follow-up after 4 years, precluding a longer period of surveillance. Patient characteristics and descriptive data are tabulated in [Table 1]. Females accounted for 66.3% of patients, and the mean age was 49.9-years-old. Headache (89.9%), tinnitus (92.1%), and hearing loss (71.9%) were the most common symptoms. Fifty-eight out of 89 patients had a new diagnosis of VS and no previous interventions. Histopathology of schwannoma was confirmed in 27 out of 89 cases. The mean maximal diameter of the tumor was 20.7 ± 5.6 mm. On MRI, Koos Grades II and III were reported in 42.7% and 46.1%. No patient presented peritumoral edema before RGK treatment. Regarding hearing function, Gardner-Robertson Grade III and Grade IV, V accounted for 50.6% of the cohort. The mean duration of follow-ups was 40.6 ± 13.3 months. The mean radiation dose was 13.5 ± 0.9 Gy and the mean shot was 6.2 ± 4.4 shots. In radiological follow-ups, the mean maximal diameter of tumor gradually decreased to 19.8 ± 4.7 mm at 1-year post treatment, 18.5 ± 5.9 mm at 2-year post treatment and 17.6 ± 4.1 mm at 3-year post treatment [Table 2] and [Figure 1].

Outcomes

Headache, tinnitus, and vertigo improved significantly post treatment [Table 3]. Two cases (2.2%) had pre treatment obstructive hydrocephalus and received ventriculoperitoneal shunt before RGK treatment. No new-onset hydrocephalus was present at post treatment follow-ups. New-onset hearing impairment was reported in 15 cases [Table 3]. We noted four new-onset facial nerve palsy after radiosurgery. The hearing function and vestibular function were preserved in 70.3% and 68.9%, respectively. The facial and trigeminal nerve preservation rates were 94.4% and 73.3%, respectively [Tables 4]. Radiation dose ≤13Gy had a significantly higher rate of facial nerve and hearing preservation than radiation doses >13Gy [Table 5].

Regarding post treatment complaints, insomnia (31.4%), anorexia (22.5%), and headache (20.2%) were the most common [Table 6]. These complaints occurred in a short-term period and then disappeared spontaneously. Four cases underwent surgical resection due to progressive tumor growth while on follow-up. Overall, radiological tumor control at 1-year, 2-year, 3-year, 4-year and 5-year post treatment was 100%, 98.8%, 98.7%, 96.6%, and 95.5%, respectively, [Figure 2].
DISCUSSION

KEY RESULTS

For 4 years, 89 patients with VS were treated by RGK. The mean radiation dose was $13.5 \pm 0.9$ Gy. The mean duration of follow-ups was $40.6 \pm 13.3$ months. The radiological tumor control rate was 95.5% at 4-year post treatment. The most relieving symptoms were headache (89.9–5.6%) and tinnitus (92.1–52.8%). The hearing function and vestibular function were preserved in 70.3% and 68.9%, respectively. The facial and trigeminal nerve preservation rates were 94.4% and 73.3%, respectively.

Interpretations

Radiation dose selection and tumor control rate

Prescription doses must balance between late perilesional toxicity and effective tumor control. In theory, low-dose rates may reduce focal toxicity by better preserving surrounding normal tissues, potentially compromising tumor control. In our study, the mean radiation dose was $13.5$ Gy (range 10–16 Gy). This is in good agreement with Lunsford (mean 13 Gy), Boari (mean 13 Gy, range 11–15 Gy), Bailo and Smith (mean 12 Gy, range 11–16.8 Gy). In these studies, tumor control rates ranged from 95% to 98% for primary VS and approximately 90% for residual and recurrent...
However, low-dose radiosurgery of Huang (mean 11 Gy, range 10–12 Gy),[13] Horiba (mean 11.9 Gy, range 11–12 Gy),[21] and Schumacher (mean marginal dose 11 Gy)[27] had lower tumor control rate (91–93%). Andrew et al. reported tumor control rate at 5-year post treatment was 91%, at mean radiation doses of 11 Gy.[2]

**Functional neurological preservation**

[Table 7] illustrates the recent results of cranial nerve function preservation after low-dose GKRS for VSs. [28,27,12,3,19,5] Regarding hearing function, Gardner-Robertson Grade III-V accounted for 50.6%. New-onset hearing
impairment was reported in 15/89 cases. This is consistent with Ignacio’s findings. The hearing function was worse in postoperative patients than in non-operative patients.\[^{6}\] According to Regis’s study, hearing function preservation was 84%, and tumor control rates were 97%.\[^{25}\] Horiba illustrated that Gardner-Robertson hearing class before irradiation, Koos tumor stage, the extension of the tumor up to fundus, the nerve of tumor origin, presence of cystic changes in the tumor, and cochlea dose demonstrated no statistically significant association with preservation of the serviceable hearing after radiosurgery.\[^{12}\] Coughlin’s systematic review also proved that the hearing preservation rate was not dependent on tumor size, patient age, radiotherapy technique, fractionation, or SRS dose. However, hearing preservation rates changed significantly during follow-ups after radiotherapy.\[^{7}\]

Pretreatment facial nerve palsy was observed in 24.7% of cases, in which 23.6% of patients had a previous surgical resection. Notwithstanding this, new-onset of transient facial nerve palsy post treatment was reported in four cases with one case recovering after 24 months. The latter is also in keeping with findings from other groups where facial nerve preservation was in the range of 95–100%.\[^{3,5,20,24,27}\] However, in residual and recurrent VS, the new-onset facial nerve palsy following GKRS might prove higher (8.9%).\[^{4}\]

Due to posterior compression of VS, 3/89 (3.3%) cases had a new-onset of trigeminal neuralgia. This value was scarcely distinguishable from previous results.\[^{3,5,20,27}\] In contrast, in residual and recurrent VS, pre treatment trigeminal neuralgia was 28.9%, and 5.6% of cases had new-onset trigeminal neuralgia post treatment. The patients with a VS >30 mm in a maximum axial diameter had a slightly higher risk of trigeminal neuralgia than those with a VS <30 mm \( (P = 0.092)\).\[^{4}\]

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**Table 6:** Temporary post treatment complaints of rotating gamma knife for vestibular schwannoma.

| Post treatment complaints       | Frequency (%) |
|---------------------------------|---------------|
| Insomnia                        | 28 (31.4)     |
| Mouth dryness                   | 15 (16.8)     |
| Anorexia                        | 20 (22.5)     |
| Alopecia                        | 6 (6.7)       |
| Seizures                        | 10 (11.2)     |
| Bleeding                        | 6 (6.7)       |
| Skin inflammation               | 3 (3.4)       |
| Nausea and vomiting             |               |
| Worsen                          | 10 (11.2)     |
| New-onset                       | 6 (6.7)       |
| Headache                        |               |
| Worsen                          | 14 (15.7)     |
| New-onset                       | 4 (4.5)       |

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**Table 7:** Preservation of cranial nerve function after low-dose Gamma Knife radiosurgery for vestibular schwannomas.

| Author, year of publication | Marginal dose (Gy) | Length of follow-up (months) | Rates of hearing preservation | Rates of facial nerve preservation | Rates of trigeminal nerve preservation |
|-----------------------------|--------------------|-----------------------------|-------------------------------|-----------------------------------|---------------------------------------|
| Smith et al., 2019\[^{28}\] | 12                 | 29.8                        | 72.2%                         | 90%                               | 79.2%                                 |
| Schumacher et al., 2017\[^{27}\] | 11                | 42                          | 56%                           | 100%                              | 96.7%                                 |
| Horiba et al., 2016\[^{22}\] | 11.9               | 24–99 (median, 56)          | 57%                           | -                                 | -                                     |
| Bailo et al., 2016\[^{8}\]  | 13                 | 79.4                        | 31.3% (66.7% among patients with Gardner-Robertson I) | 94.9%                           | 93.2%                                 |
| Lipski et al., 2015\[^{19}\] | 11–12 (mean, 11.5) | 24–84 (median, 48)         | 77%                           | 100%                              | 100%                                  |
| Boari et al., 2014\[^{5}\]   | 11–15 (median, 13) | 36–157 (mean, 75.7)       | 49%                           | 98.9%                             | 98.2%                                 |
| Our series                   | 13.5               | 40.6                        | 70.3%                         | 94.4%                             | 73.3%                                 |
Complications

Regarding the safety of RGK, no mortality case was reported even in elderly patients with severe comorbidities. Insomnia (31.4%) and anorexia (22.5%) were the most common complaints. Nevertheless, headache, insomnia, and anorexia were usually relieved by medication (usually within three days). Despite this, symptoms lasted up to 1 month in some patients. Brain edema was determined by magnetic imaging resonance. In this context, edema was reported as a complication of radiosurgery when it got worse or fully evolved after treatment, usually at a rate of 3-month post radiosurgery. In this study, eight cases had post treatment brain edema (21.6%), generally presenting with headache, nausea, and vomiting. All of all these particular cases were treated with corticoid therapy and their symptoms relieved after several weeks to 1 month. This is also in keeping with Baio et al., observing signs of adverse radiation effect in 6/59 cases.[10] However, the studies from Schumacher et al. showed no complications in any of their patients, including hydrocephalus, radionecrosis, or cystic tumor cavitation.[27] Boari denied malignant transformation and radiation-induced tumors occurred during follow-up.[13]

Limitations

It is plausible that several limitations might have influenced the results obtained. The first limitation was a small number of patients and a relatively short follow-up after radiosurgery. Inherent selection biases associated with nonrandomized treatment assignments were another flaw. Despite that, prospective data gave reasonable tumor control and cranial nerve function preservation rates compared to previously published reports. Another drawback was the loss of patients to follow-up over time. Patients’ compliance at long-term follow-up was variable, particularly for patients living far from our center and the poor patients; this limitation could not be easily overcome, even by scheduling subsequent examinations at hospital discharge.

CONCLUSION

In this group of patients, RGK proved to be effective and safe in the management of VS mearing <3 cm. Tumor control throughout follow-up was comparable to other studies; no significant neurological complications were observed at long-term either. Further multicentric prospective studies with larger cohorts are warranted to validate the findings of this paper.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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