Fate of Residual Tumor After Subtotal-resected, Previously-irradiated Vestibular Schwannoma: Long-term Follow-up of a Single Institutional Series

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**Abstract**

**Background:** The fate of residual tumor after salvage surgery for recurrent vestibular schwannoma (VS) after radiosurgery has not been elucidated. We reviewed our surgical series of salvage surgery for recurrent VS and the natural history of the residual tumor after salvage surgery.

**Methods:** This study enrolled 14 patients who were received salvage surgical resection in our institute and were followed-up for >12 months.

**Results:** There were 3 male and 11 female patients with a median age of 55 years (range: 16-70). The pre-SRS tumor volume was a median 6591 mm$^3$. All patients were treated by GKS. The median duration from GKS to surgery was 52 months (range: 10-116). Solid tumor growth was observed in 6 (42.9%) patients and cyst formation was observed in 8 patients (57.1%). Subtotal resection was performed in 13 (92.9%) patients and gross total resection was achieved in only one (7.1%) patient. Postoperative facial paresis occurred in 5 (35.7%) patients. Postoperative surgical complications occurred in 2 (14.3%) patients. After salvage resection for irradiated VS, no patient showed tumor progression or recurrence during the follow-up period (13 subtotal resection and 1 total resection). In addition, 2 patients in the subtotal resection group showed residual tumor shrinkage after salvage surgery during the follow-up period.

**Conclusion:** The behavior of residual tumors after salvage surgery for irradiated VS was stable. Adjuvant treatment for these residual tumors may not be necessary.

**Introduction**

Stereotactic radiosurgery (SRS) is the popular treatment for small to medium-sized vestibular schwannoma (VS). In recent studies, the control rate of VS after SRS is 90% and its complication rate was 1~4%. Temporary tumor expansion after SRS occurred in 11 to 74% of cases; however, most of these cases could be managed conservatively. Although SRS showed excellent clinical outcomes, recurrence could happen in some cases. In some recurrent cases, salvage microsurgical resection is necessary to relieve the local mass effect and the intracranial hypertension. Microsurgery of irradiated-VS is difficult due to the radiation effect, including tumor texture changes and neurovascular adhesions. This difficult surgery leads to a high possibility of residual tumor and postoperative complications. For residual tumors after salvage surgery, adjuvant treatment may be considered to prevent regrowth of the tumor. However, there has been a great deal of controversy about the need for adjuvant treatment of subtotal-resected, previously irradiated VS. Herein, we present our experience of salvage surgery for recurrent vestibular schwannoma after radiosurgery.

**Materials And Methods**

**2-1. Patient population**

The study protocol and review of medical records were approved by the institutional review board of Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. Between January 2005 and December 2019, 788 patients with a presumed diagnosis of vestibular schwannoma (VS), based on radiologic analysis, were treated by gamma-knife radiosurgery (GKS) in our institution. Among these patients, 14 (1.7%) underwent salvage surgery during the follow-up period. This study enrolled 14 patients who received salvage surgical resection in our institution and were followed up for >12 months. Follow-up included brain magnetic resonance imaging (MRI), initially at 6 months or 1 year after SRS and then every 1 or 2 years until tumor growth requiring therapeutic intervention was observed.

GKS was performed using a Leksell gamma knife model B (April 1990 to March 2004), Leksell GK Model C (March 2004 to November 2011) or a Leksell GK perfexion (December 2011 until the present). Dose planning for the GKRS treatments used MRI analysis in the Leksell gamma plan. The Elekta and marginal prescription dose was from 12 to 13 Gy.

**2-2. Measurements of tumor volume and growth rate**

At each follow-up examination, all tumors were volumetrically measured during enhanced MRI using 1.5 to 3 mm thick slices; the slices were processed using software developed in-house (AsanJ, based on a plug-in package for ImageJ (http://rsbweb.nih.gov/ij)). To minimize measurement error, the volume of each tumor was measured three times by three different board-certified neurosurgeons at each follow-up visit, and the mean value at each visit was recorded. Growing tumors were defined as those showing a 33% increase in volume from baseline, corresponding approximately to a 10% increase in diameter.

The follow-up period was defined as the interval between the dates of the initial and last brain MRI.

All statistical analyses were performed using PASW Statistics for Windows, version 24.0 (IBM Corp., Armonk, New York, USA) and R-3.0.2 statistical software (http://www.r-project.org), with a p value <0.05 considered statistically significant.

**Results**

There were 3 male and 11 female patients with a median age of 55 years (range: 16-70). The median pre-SRS tumor volume was 6591 mm$^3$. All patients were treated by GKS. The median duration from GKS to surgery was 52 months (range: 10-116). Solid tumor growth was observed in 6 (42.9%) patients and cyst formation was observed in 8 patients (57.1%). Subtotal resection was performed in 13 (92.9%) patients, and gross total resection was achieved in only one (7.1%) patient. Postoperative facial paresis occurred in 5 (35.7%) patients. Postoperative surgical complications occurred in 2 (14.3%) patients. The median follow-up period was 48 months (12-112). Representative patient MR findings are presented in Figure 1. Details of the patients' characteristics are presented in Table 1.
According to the surgical records, the irradiated tumors had a relatively hard and firm texture compared to non-irradiated tumors. Identification of facial nerves was not too difficult; however, it was difficult to dissect them from the tumor capsule. Most of the tumor was adherent to the cerebellum and brainstem and the dissection plane between the tumor and neural structure was not well preserved. Also, arachnoid membrane thickening could be seen around the tumor. A representative intraoperative image is shown in Figure 2.

We analyzed the tumor growth after SRS and the size of the residual tumor after salvage surgery. The pattern of tumor growth after SRS was varied (Figure 3-A). Six of 14 (42.8%) tumors showed solid tumor growth, while 8 of 14 (57.1%) showed peritumoral cyst formation or internal cyst formation.

Thirteen of 14 (92.9%) patients underwent subtotal resection. The median residual tumor volume was 2346 mm$^3$ (range: 334-9059 mm$^3$) and the mean degree of resection was 85.7% (43.0-98.4%). Postoperative facial weakness occurred in 5 (35.7%) patients. Postoperative cerebellar swelling or infarction occurred in 2 (14.2%) patients.

After salvage resection for irradiated VS, no patient showed tumor progression or recurrence during the follow-up period (13 subtotal resection and 1 total resection). In addition, 2 patients in the subtotal resection group showed residual tumor shrinkage after salvage surgery during the follow-up period (Case #3 and Case #6 in Table 2). Details of the enrolled patients’ clinical characteristics are presented in Table 2 and tumor growth after the salvage surgery is presented in Figure 2.

**Discussion**

The treatment options for VS are microsurgery, SRS and ‘wait and watch’. The natural history of untreated VS has been reported. Paldor et al. reported that the average growth rate of VS was 0.99-1.11 mm/year. Considering the slow growth of VS, small asymptomatic tumors could be managed by a wait and watch strategy. However, Regis et al. reported that over 70% patients who were managed by wait and watch eventually needed treatment. Also, Prasad et al. reported that 26% of patients treated conservatively eventually underwent surgery and over 40% of patients lost hearing function during the wait and watch period. Thus, in clinical practice, treatment is usually recommended for VS to arrest the tumor growth.

SRS has shown favorable treatment outcomes for small to medium sized tumors. A favorable control rate of SRS for VS has been reported. Hasegawa et al. reported long term outcomes of VS treated by gamma knife surgery and the ten-year actuarial progression-free survival of GKS-treated VS was 87%. Although SRS showed good tumor control of VS, treatment failure of SRS was almost inevitable. The risk factors of failure of radiosurgery are a large tumor volume, a young age and neurofibromatosis type 2 association. In the previous report of Hasegawa et al., a tumor volume over 10 cm$^3$ was the only predictor of treatment failure. The SRS-treatment failure cases need salvage treatment. The salvage treatment options for recurrent VS after SRS are salvage radiosurgery and microsurgery. Fu et al. reported favorable outcomes of re-irradiation for recurrent VS; however, the volume of the recurrent tumors were small and the post-SRS complications were high.

In cases of a rapidly growing tumor, a tumor with a mass effect, or a cyst enlarging tumor, salvage microsurgery is a more suitable treatment than radiosurgery or radiotherapy. Microsurgical resection of irradiated VS is difficult. Difficult dissection is encountered in over 90% of cases and there is a high rate of worsening of facial nerve function, and for these reasons, complete excision of the tumor is difficult.

In our experience, irradiated VS tumor is densely adherent to neural and vascular structures, thus defining the dissection plane between the tumor and normal tissue is difficult (Figure 3). For this reason, to minimize postoperative complications, subtotal tumor resection may be necessary. In our series, total resection could be achieved in only one patient and facial nerve paresis occurred in 35.7% of the patients.

For residual tumor after salvage surgery, there is controversy about the necessity of the treatment of the residual tumor. Adjuvant radiosurgery after subtotal resection for VS shows excellent tumor control. Redo-SRS may be only option for residual tumor after salvage microsurgery after SRS; however, irradiation-induced complications include necrosis, and malignant transformation may be a worrisome problem.

The fate of the residual tumor after microsurgery for VS has been reported. Park et al. reported the natural history of residual tumor after subtotal resection for VS. In their report, a large proportion of residual tumors were stable; however, 17% of tumors showed regrowth. They suggested the reasons for the stability of the residual tumor was tumor devascularization during surgery. Chen et al. reported that there was no growth after near total resection for VS; however, all cases of subtotal-resected tumor showed tumor growth. Thus, there is debate about the necessity of adjuvant treatment for residual tumor after salvage surgery for irradiated VS.

In our series, there was no regrowth of residual tumor during the median 4 years follow-up period. Moreover, 2 tumors in our series showed tumor shrinkage after salvage resection. Shuto et al. reported that in 12 consecutive cases of salvage surgery for VS, 11 of 12 patients’ residual tumors were stable, and 8 of 12 patients’ residual tumors showed tumor shrinkage without adjuvant treatment. An effect of the prior radiation may still exist after salvage resection. These results could be interpreted to mean that the residual tumor after salvage surgery was more stable than a not-irradiated tumor.

Redo-radiosurgery may be safer than salvage surgery when it comes to acute complications. However, SRS has a high risk of radiation injury. Considering the benign nature of VS, the stability of the residual tumor, and the high risk of radiation injury, residual tumor after salvage surgery for irradiated VS could be managed with a ‘first leave them alone’ strategy.

**Limitations**
Due to the rarity of cases, our study contains only 14 patients. This study was also retrospectively designed, which thus precludes a fully meaningful analysis, as it could possibly be subject to selection bias. Additionally, this is a single institutional series spanning a 15-year study period, and the variable length of the follow-up data means that it is difficult to reveal the definitive fate of residual tumor after salvage surgery and draw definite conclusions about the best treatment strategies. However, this study is valuable since it reviewed the natural history of residual tumors after salvage surgery for irradiated VS in a single institute, so our results may become a reference study for future meta-analysis or prospective studies.

Conclusion
Residual tumors after salvage surgery for irradiated VS were stable. It is difficult to perform total resection of irradiated VS and the risk of postoperative facial paresis is high due to the effects of previous radiation. Adjuvant treatment of these residual tumors may not be necessary, but additional large studies or meta-analyses are necessary to confirm this conclusion.

Declarations
The authors declare no competing interests regarding this study.

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Availability of data and material
The data supporting the findings of this study are included in the article and its supplementary material file.

Authors’ contributions
Author contributions JB and YHK conceived and designed the study. SWS and CKH conducted the literature search. JB, YHK, SWS and CKH were involved in the analysis and interpretation of data. JB drafted the manuscript. The study was supervised by CKH and JHK. All authors read and approved the final manuscript.

Ethics approval
This retrospective study has been approved by the appropriate ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. (Approval by IRB of Asan Medical Center, No. 2021-1137). For this type of study, formal patient consent is not required. The IRB of Asan Medical Center gave the right of exemption of ‘informed consent’ for this study. The reason described below.

The risk expected from this ‘retrospective observational study’ is not greater than the Level I risk. In addition, all of included patients’ dataset were anonymized. There is no reason to presume the refusal of the research subject’s consent, and the risk to the enrolled patients is extremely low even if consent is waived. Consent exemption does not infringe on the rights or welfare of the subject. It is not the research for drug/medical device approval, and it is not a research regulated by a foreign regulatory agency.

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References
1. Kalogeridi, M.-A., Kougioumtzopoulou, A., Zygogianni, A. & Kouloulias, V. Stereotactic radiosurgery and radiotherapy for acoustic neuromas. Neurosurgical Review 43, 941-949 (2020).
2. Buss, E. J., Wang, T. J. C. & Sisti, M. B. Stereotactic radiosurgery for management of vestibular schwannoma: a short review. Neurosurgical Review 44, 901-904 (2021).
3. Langenhuizen, P. P. J. H. et al. Prediction of transient tumor enlargement using MRI tumor texture after radiosurgery on vestibular schwannoma. Medical Physics 47, 1692-1701 (2020).
4. Shuto, T., Inomori, S., Matsunaga, S. & Fujino, H. Microsurgery for vestibular schwannoma after gamma knife radiosurgery. Acta Neurochirurgica 150, 229-234 (2008).
5. Lee, C.-C. et al. Microsurgery for vestibular schwannoma after Gamma Knife surgery: challenges and treatment strategies. Journal of Neurosurgery 121, 150-159 (2014).
6. Byun, J. et al. Growth rate and fate of untreated hemangioblastomas: clinical assessment of the experience of a single institution. Journal of Neuro-Oncology 144, 147-154 (2019).
7. Paldor, I., Chen, A. S. & Kaye, A. H. Growth rate of vestibular schwannoma. Journal of Clinical Neuroscience 32, 1-8 (2016).
8. Prasad, S. C. et al. Decision Making in the Wait-and-Scan Approach for Vestibular Schwannomas: Is There a Price to Pay in Terms of Hearing, Facial Nerve, and Overall Outcomes? Neurosurgery 0 (2017).
9. Régis, J. et al. Wait-and-see strategy compared with proactive Gamma Knife surgery in patients with intracanicular vestibular schwannomas. *Journal of Neurosurgery* **113**, 105-111 (2010).

10. Chen, Z. et al. The behavior of residual tumors and facial nerve outcomes after incomplete excision of vestibular schwannomas. *Journal of Neurosurgery* **120**, 1278-1287 (2014).

11. Husseini, S. T. et al. Salvage surgery of vestibular schwannoma after failed radiotherapy: The Gruppo Otologico experience and review of the literature. *American Journal of Otologyngology-Head and Neck Medicine and Surgery* **34**, 107-114 (2013).

12. Hasegawa, T. et al. Long-term outcomes in patients with vestibular schwannomas treated using gamma knife surgery: 10-year follow up. *Journal of Neurosurgery* **102**, 10-16 (2005).

13. Fu, V. X. et al. Retreatment of vestibular schwannoma with Gamma Knife radiosurgery: clinical outcome, tumor control, and review of literature. *Journal of Neurosurgery* **129**, 137-145 (2018).

14. Radwan, H., Eisenberg, M. B., Knisely, J. P. S., Ghaly, M. M. & Schulder, M. Outcomes in Patients with Vestibular Schwannoma after Subtotal Resection and Adjuvant Radiosurgery. *Stereotactic and Functional Neurosurgery* **94**, 216-224 (2016).

15. Park, H. H. et al. The behavior of residual tumors following incomplete surgical resection for vestibular schwannomas. *Scientific Reports* **11** (2021).

**Tables**

**Table 1. Basal characteristics of the patients undergoing surgery after radiosurgery for vestibular schwannoma**

|                         | N (%)                        |
|-------------------------|------------------------------|
| **Sex**                 |                              |
| Male                    | 3 (21.4%)                    |
| Female                  | 11 (78.6%)                   |
| **Age (years)**         | 55 (16-70)                   |
| **Initial tumor volume (mm$^3$)** | 6591 (1689-14689) |
| **Koo’s grade**         |                              |
| 2                       | 3 (21.4%)                    |
| 3                       | 5 (57.1%)                    |
| 4                       | 6 (42.9%)                    |
| **NF association**      | 0                            |
| **Modality of SRS**     |                              |
| GKS                     | 14 (100%)                    |
| **Duration from SRS to surgery (months)** | Median 52 (10-116) |
| **Recurrence pattern**  |                              |
| Solid growth            | 6 (42.9%)                    |
| Cyst formation          | 8 (57.1%)                    |
| **Extent of resection** |                              |
| Gross total resection   | 1 (7.1%)                     |
| Subtotal resection      | 13 (92.9%)                   |
| **Postoperative facial palsy (6 months)** |                     |
| House-Brackmann grade   |                              |
| Grade 1                 | 9 (64.3%)                    |
| Grade 2                 | 2 (14.3%)                    |
| Grade 4                 | 3 (21.4%)                    |
| **Postoperative complication** | 2 (14.3%)            |
| Cerebellar hemorrhage/infarction | 2                      |
| Recurrence after surgery| 0                            |
| **FU duration after surgery (months)** | Mean 48 (12-112) |

NF: neurofibromatosis, SRS: stereotactic radiosurgery, GKS: gamma-knife surgery, FU: follow-up
Table 2. Detailed characteristics of the enrolled patients.

| Case | Age/Sex | Tumor volume (mm³) | Tumor type | Koo's grade | Hearing status | SRS modality/dose (isodose line 50%) | Recurrence pattern | Time from SRS to surgery (months) | Preop. Tumor volume (mm³) | EOR | Preop/Postop. (6 months) | H-B grade |
|------|---------|---------------------|------------|-------------|----------------|--------------------------------------|-------------------|-------------------------------|---------------------------|-----|-------------------------|-----------|
| 1    | 70/F    | 4,600               | Solid      | 3           | non-serviceable | GK/12Gy Solid growth                 | 72                | 17,991                        | STR 525 (97%)             | 1/4 |                         |           |
| 2    | 44/F    | 2,300               | Solid      | 2           | non-serviceable | GK/12Gy Solid growth                 | 116               | 6,077                         | STR 966 (84%)             | 1/4 |                         |           |
| 3    | 67/F    | 4,500               | Solid      | 2           | non-serviceable | GK/12Gy Cyst formation               | 10                | 41,797                        | STR 7351 (82%)            | 1/1 |                         |           |
| 4    | 66/F    | 14,300              | Solid+Cystic | 4           | non-serviceable | GK/9Gy Cyst formation                | 31                | 23,833                        | STR 1292 (94%)            | 1/2 |                         |           |
| 5    | 46/F    | 2,523               | Solid      | 3           | non-serviceable | GK/12Gy Cyst formation               | 38                | 10,400                        | STR 827 (92%)             | 1/1 |                         |           |
| 6    | 62/M    | 5,500               | Solid+cystic | 3           | non-serviceable | GK/12Gy Solid growth                 | 36                | 12,313                        | STR 730 (94%)             | 1/1 |                         |           |
| 7    | 49/M    | 10,100              | Solid      | 4           | non-serviceable | GK/12Gy Cyst formation               | 93                | 19,517                        | STR 4120 (78%)            | 1/1 |                         |           |
| 8    | 16/F    | 5,113               | Solid      | 4           | non-serviceable | GK/12Gy Solid growth                 | 50                | 11,786                        | STR 1110 (90%)            | 1/1 |                         |           |
| 9    | 56/F    | 7,400               | Solid      | 4           | Serviceable    | GK/12Gy Cyst formation               | 63                | 15,900                        | STR 9059 (43%)            | 1/1 |                         |           |
| 10   | 64/F    | 1,689               | Solid      | 2           | non-serviceable | GK/12Gy Cyst formation               | 20                | 9,451                         | STR 2556 (72%)            | 1/1 |                         |           |
| 11   | 43/F    | 4,900               | Solid      | 3           | non-serviceable | GK/13Gy Solid growth                 | 54                | 10,951                        | GTR 0                     | 1/2 |                         |           |
| 12   | 59/M    | 6,600               | Solid      | 4           | non-serviceable | GK/13Gy Cyst formation               | 41                | 12,556                        | STR 1237 (90%)            | 1/1 |                         |           |
| 13   | 52/F    | 14,689              | Solid      | 4           | non-serviceable | GK/10Gy Solid growth                 | 49                | 22,342                        | STR 746 (96%)             | 1/4 |                         |           |
| 14   | 54/F    | 8,068               | Solid      | 3           | non-serviceable | GK/12Gy Cyst formation               | 64                | 20,968                        | STR 334 (98%)             | 1/1 |                         |           |

SRS: stereotactic radiosurgery, GK: gamma-knife surgery, EOR: extent of resection, GTR: gross total resection, STR: subtotal resection

Figures
Representative case of salvage surgery for recurrent tumor after gamma-knife radiosurgery Legend: (A) MRI findings of a 63-year-old female patient who underwent salvage surgery after gamma knife radiosurgery for vestibular schwannoma (A). She came to clinic for hearing loss, and MRI showed a lobulated mass in the right cerebellopontine angle. She underwent gamma knife radiosurgery (dose: 13 Gy). (B) One year after radiosurgery, she came to the emergent department due to headache and MRI showed a newly developing peritumoral cyst that was compressing the brainstem and cerebellum. (C) She underwent salvage subtotal resection to decompress the mass effect. (D) The residual tumor was stable for 6 years of follow-up. The tumor size was decreased during the follow-up (E-H) of a 58-year-old male patient who underwent salvage surgery after gamma knife radiosurgery for vestibular schwannoma. (E) He came to our clinic for tinnitus. MRI showed a well delineated mass in the left cerebellopontine angle. He underwent gamma knife radiosurgery (dose: 12 Gy). (F) Three years later, an increased size of the mass was noted and it compressed the brainstem and cerebellum. (G) He underwent salvage subtotal resection to decompress the mass effect. (H) The residual tumor was stable for 9 years of follow-up. The tumor size decreased during the follow-up period.
Figure 2

Intraoperative findings of salvage resection after radiosurgery for vestibular schwannoma. Legend: Intraoperative images of a 43-year-old female patient who underwent salvage surgery for vestibular schwannoma after radiosurgery. Retrosigmoid craniotomy was performed. (A) A thick tumor capsule and arachnoid adhesion was noted. The AICA was adherent to the tumor capsule. (B) The AICA was meticulously dissected from the tumor and an arachnoid-tumor-choroid plexus adhesion was noted. The tumor was very hard and adhesiolysis was performed. (C) There was no clear demarcation between the tumor and the trigeminal nerve. It could not be dissected due to the severe adhesion. (D) The tumor capsule is severely adherent to the brainstem, so subcapsular subtotal tumor resection was performed. AICA: anterior inferior cerebellar artery

Figure 3

(A) Volume change after radiosurgery

(B) Volume change after salvage surgery
Spaghetti plot of the volume change after radiosurgery and salvage surgery for vestibular schwannoma Legend: (A) Spaghetti plot of the preoperative volume change after radiosurgery. The tumor size gradually increased; however some tumor showed an abrupt cystic volume increase. (B) Spaghetti plot of the postoperative volume change after salvage surgery for irradiated VS.

Supplementary Files

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