Repeted Delayed Onset Cerebellar Radiation Injuries After Linear Accelerator-Based Stereotactic Radiosurgery for Vestibular Schwannoma
—Case Report—

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Abstract
A 63-year-old woman presented with right hearing disturbance and vertigo. Magnetic resonance (MR) imaging revealed the presence of right vestibular schwannoma (VS). Stereotactic radiosurgery (SRS) was performed with a tumor marginal dose of 14 Gy using two isocenters. She was followed up clinically and neuroradiologically using three-dimensional spoiled gradient-echo MR imaging. She experienced temporal neurological deterioration due to peritumoral edema in her right cerebellar peduncle and pons for a few months beginning 1.5 years after SRS, when she experienced transient right facial dysesthesia and hearing deterioration. Ten years after SRS, the patient presented with sudden onset of vertigo, gait disturbance, diplopia, dysarthria, and nausea. MR imaging demonstrated a new lesion in the right cerebellar peduncle, which was diagnosed as radiation-induced stroke. The patient was followed up conservatively and her symptoms disappeared within a few months. Multiple delayed onset radiation injuries are possible sequelae of SRS for VS.

Key words: brain edema, radiation injury, stereotactic radiosurgery, stroke, vestibular schwannoma

Introduction
Vestibular schwannoma (VS) is a benign neoplasm arising from the vestibular nerves in the cerebellopontine angle and internal acoustic meatus. Conventionally, these tumors have been treated using resection or close observation. Stereotactic radiosurgery (SRS) has been offered to patients with VS as an alternative to surgical removal because of the lower morbidity and better tumor control compared to resection.7,12 The advantages 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. Therefore, changes in the tumor and complications of the surrounding normal tissue after radiosurgery should be carefully followed up over a long period of time.

Approximately 5% of patients who receive 45–60 Gy during conventional radiotherapy will experience a complication in the irradiated normal tissue within 5 years.9 However, a cohort long-term follow-up study of benign neoplasms found the incidence of radiation necrosis was about 29%, and the latency period ranged from 2 months to 19 years.11 In the radiosurgical setting, an estimated 3% dose-based risk was derived using a linear quadratic model.11 On the other hand, biological equivalent dose estimation based on the linear quadratic model may be inappropriate in the hypofractionated settings.15,20 Consequently, no predominant guidelines for late reactions have been established in the field of hypofractionated stereotactic irradiation. Late-onset complications after stereotactic irradiation include radiation-induced edema, radiation necrosis, cyst formation, radiation-related tumorigenesis, and radiation-induced cerebrovascular injury.1,2,4,6,10,18,25,29,30

We describe a rarely predictable delayed complication which occurred after SRS in a patient with VS.

Case Report
A 63-year-old, otherwise healthy, woman presented with mild right hearing disturbance and vertigo. T1-weighted magnetic resonance (MR) imaging with gadolinium revealed an extra-axial mass lesion in the right cerebellopontine angle, which was considered to be VS (Fig. 1A). The
tumor volume increased gradually during a one-year observation period, and the patient elected to undergo SRS. A stereotactic head ring was affixed to her head following administration of intravenous neuroleptic analgesic drugs (pentazocine and diazepam) and a local anesthetic agent (lidocaine). The SRS was performed using a Clinac 2100C (Varian Medical Systems, Milpitas, California, USA) and a convergent beam irradiation system (FL Fischer-Leibinger, Freiburg, Germany). Dose planning was designed with stereotactic treatment planning software (FL Fischer-Leibinger) based on the thin slice (3 mm) MR images. The preoperative tumor volume was 3.78 cm³ and the mean diameter was 1.9 cm. A maximal dose of 32 Gy and a tumor margin dose of 14 Gy were delivered using two isocenters (Fig. 1B). The patient experienced no acute complications and was discharged the next day, and was followed up clinically and radiologically at least annually.

To measure the tumor volume, three-dimensional spoiled gradient-echo (3D-SPGR) MR imaging with gadolinium was obtained using repetition time 45 msec, echo time 3.1 msec, field of view $180 \times 180$ mm, slice thickness 1 mm, and matrix $256 \times 160$. Computer-assisted measurement was used to calculate the tumor area on each MR image. The volume was determined as a volume change of more than 20%. The lesion demonstrated transient volume increases and decreases (Fig. 2). As a result, the patient experienced transient facial dysesthesia and deterioration of her hearing disturbance without facial palsy or ventriculomegaly 1.5 years after SRS. These symptoms were classified as grade 2 of the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE ver 3.0). MR imaging revealed tumor swelling and transient peritumoral edema in the right cerebellar peduncle and pons at this time (Fig. 1C, D). Corticosteroids were administered orally and these subacute symptoms disappeared gradually. The tumor decreased in size, the hyperintense lesion had disappeared within 6 months, and no other adverse effects were found by MR imaging during the 9 years after SRS.

FIG. 1 A: T₁-weighted magnetic resonance (MR) image with gadolinium revealing an extra-axial mass lesion in the right cerebellopontine angle. B: Stereotactic radiosurgery plan describing the isodose lines (5, 10, and 14 Gy). The dotted line indicates the planned target volume. C, D: T₁-weighted with gadolinium (C) and T₂-weighted (D) MR images demonstrating transient enlargement of the tumor, with a hyperintense lesion on T₂-weighted image (arrow), in the right cerebellar peduncle and pons. E, F: T₁-weighted with gadolinium (E) and T₂-weighted (F) MR images obtained 9 years after the SRS, just before the late onset complication, revealing no significant complications.

FIG. 2 Tumor volume chart indicating tumor enlargement and shrinkage over a period of more than 10 years. Only the second peak (arrowhead) was significant enlargement based on our criteria (more than 20% increase compared to the former reference volume).

FIG. 3 A, B: Magnetic resonance (MR) images obtained 3 days after the onset of the second radiation-related injury showing a new lesion in the right cerebellar peduncle without tumor enlargement as hyperintense on T₂-weighted image (A, arrow) and nonehanced isointense on T₁-weighted image with gadolinium (B). C–F: Three-dimensional spoiled gradient-echo MR images showing a hypointense lesion in the right cerebellar peduncle (arrows), and the right anterior inferior cerebellar artery with no signal gap (arrowheads). G, H: Follow-up MR images 6 months after the second complication showing the lesion with mild shrinkage on T₂-weighted image (G, arrow) and nonehanced hypointense on T₁-weighted image with gadolinium (H, arrow).
(Fig. 1E, F). The steroid therapy was tapered in a few months, and she resumed her daily life without clinical exacerbation.

Ten years after the SRS, the patient presented with vertigo, gait disturbance, diplopia, dysarthria, and nausea, all grade 2 symptoms of CTCAE ver 3.0, and was admitted to hospital. MR imaging performed at our institute demonstrated a new lesion in the right cerebellar peduncle without tumor enlargement as hyperintense on T2-weighted images, isointense on T1-weighted images without and with gadolinium, and mildly hypointense on 3D-SPGR images with gadolinium (Fig. 3A–C, F). There was no signal gap in the right anterior inferior cerebellar artery (AICA) (Fig. 3D–F). Diffusion-weighted images were not obtained. This lesion was diagnosed as radiation injury and the patient was treated conservatively. She resumed her daily activity within a few weeks, and her symptoms disappeared gradually within a few months. MR imaging study revealed the lesion with mild shrinkage on T2-weighted images, hypointense on T1-weighted images, and no enhancement on T1-weighted images with gadolinium 6 months after onset of these symptoms (Fig. 3G, H).

Discussion

Radiosurgery has been used to treat patients with VS for more than two decades with good results.7,12) The local control rate was 89% in our cohort of patients, which is comparable to the results from other series (unpublished data). Therefore, the unexpected development of delayed onset complications after radiosurgery raises concerns about the long-term safety and efficacy. SRS is most commonly performed with a tumor marginal dose of 12 to 13 Gy and this was lower than the estimated 3% risk dose previously described.11) Therefore, the risk in each case might vary depending on the individual. The establishment of a prediction tool, such as biomarkers, for radiation injury is one of the ultimate goals of radiation biology research.10,20)

The incidence of radiation-induced stroke remains unknown. Extracranial internal carotid artery stenosis after irradiation for head and neck cancer, moyamoya syndrome after cranial irradiation, and radiation-induced stroke in pediatric cancer survivors are well recognized.3) In addition, perforator strokes attributable to conventional irradiation have been reported with various radiation doses,23) with cases occurring after 50 Gy over 2 months, 35.6 Gy over 35 days,25) 50 Gy over 5 weeks,14) and 49 Gy.24) Atherosclerosis may also be accelerated by irradiation, causing subsequent stroke.6,22,26) No clinical course similar to that in the present case has been reported. but is a possible sequela of radiosurgery. Although the precise pathophysiology is unknown, we believe that the interval between these complications was due to the difference in time course between the early-delayed endothelial injury leading to abnormal permeability of the blood-brain barrier and the late-delayed atherosclerosis of the perforators.20) Deoxyribonucleic acid double strand breakage, genomic instability, and subsequent gene alterations may also explain the related etiology of the radiation-induced edema and radiation-induced stroke, but more information is needed to elucidate the mechanisms underlying the development of such injuries.13,18,22,26)

In conclusion, delayed onset radiation injuries can occur multiple times in patients with VS after SRS. The present patient experienced two separate episodes of radiation-related injuries. The first was radiation-induced edema, and the second was probably radiation-induced perforator stroke. Special attention should be paid to the types of adverse effects following SRS in patients with VS.

Acknowledgment

This work was supported in part by Grant-in-Aid for Scientific Research (#23592095) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors have nothing to disclose in terms of financial support or relationships that may pose a conflict of interest.
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Neurol Med Chir (Tokyo) 52, December, 2012