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Clinical and Histopathologic Features of Recurrent Vestibular Schwannoma (Acoustic Neuroma) after Stereotactic Radiosurgery

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Objective: Stereotactic radiosurgery for vestibular schwannoma entails uncertain long-term risk of tumor recurrence and delayed cranial neuropathies. In addition, the underlying histopathologic changes to the tumor bed are not fully characterized. We seek to understand the clinical and histologic features of recurrent vestibular schwannoma after stereotactic radiation therapy.
Study Design: Retrospective review.
Setting: Tertiary referral center.
Patients: Four patients who underwent microsurgical resection of vestibular schwannoma after primary stereotactic radiation therapy.
Intervention: Patients were treated primarily with gamma knife radiosurgery or fractionated stereotactic radiotherapy followed by salvage microsurgery. Retrosigmoid craniotomy was used in all cases.
Main Outcome Measures: Histopathologic review. Preoperative and postoperative facial nerve function was assessed with the House-Brackmann scale.
Results: We observed highly inconsistent radiation changes in the cerebellopontine angle and internal auditory canal. Fibrosis outside and within the tumor bed varied markedly, complicating microsurgical dissection. Light microscopy confirmed the presence of viable tumor in all cases. Histopathologic features were typical of vestibular schwannoma, and there was no significant scarring that could be attributed to radiation effect.
Conclusions: The variable fibrosis in the cerebellopontine angle and lack of radiation changes seen histopathologically in irradiated vestibular schwannoma suggest that a uniform treatment effect was not achieved in these cases. Although all four patients with preoperative cranial neuropathies were found intraoperatively to have fibrosis in the cerebellopontine angle, excellent preservation of facial nerve anatomy and function was possible with salvage microsurgical resection. Additional analyses are needed to clarify the histopathologic and molecular characteristics associated with vestibular schwannoma growth after stereotactic radiation. **Key Words:** Microsurgical resection—Stereotactic radiation therapy—Vestibular schwannoma.
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The mainstay of vestibular schwannoma (VS) management has traditionally been microsurgical resection by an experienced neurotologic and neurosurgical team. Excellent outcomes have been reported from surgery for VS regarding anatomic preservation of the facial nerve (1–4), facial nerve function (1–5), and serviceable hearing preservation (6–11). Complete tumor removal can be achieved through meticulous microsurgical dissection, resulting in minimal morbidity and mortality (1,4,12) and favorable long-term recurrence rates ranging from 0.5 to 1.5% (3,13). Refinements in neuroanesthesia and postoperative critical care have also contributed to the safety of craniotomy and microsurgical resection for VS.

Stereotactic radiosurgery ("gamma knife") and fractionated stereotactic radiotherapy (FSR) have become increasingly popular alternatives to microsurgical resection for the primary treatment of VS. Stereotactic radiosurgery, developed by Lars Leksell in 1951 (14) and used on VS patients for the first time in 1969 (15), involves the biologic inactivation of a three-dimensional target by a single dose of ionizing radiation (16). In contrast, FSR involves multiple treatment sessions to deliver a thera-

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peutic radiation dose to the tumor. Regardless of technique, treatment-related morbidity is comparable, if not improved, in patients who receive radiation therapy compared with microsurgical resection (17–20). Because a craniotomy and general anesthesia are avoided, radiation therapy is also a reasonable alternative to surgery for the elderly or patients with symptomatic or growing tumors, who are poor surgical candidates (21).

Approximately 10 in 1 million persons in the United States are diagnosed with VS (22). Using an estimated 2001 U.S. population of 285 million persons, approximately 3,000 new cases of VS will be diagnosed in 2002. Proponents of radiation therapy predict that in 10 years, an equal number of these patients will receive either stereotactic radiation or microsurgery as the primary modality for VS (23). However, the decision to choose microsurgical resection or radiosurgery is still controversial. The obvious disadvantage with "radiosurgery" or radiotherapy is that tumor volume is not directly reduced or removed; treatment success with radiation is measured in terms of tumor growth suppression as demonstrated by serial magnetic resonance imaging (MRI). In addition, although radiation therapy for VS has shown low tumor regrowth rates ranging from 2 to 9% (24–26) with mean follow-up periods of 2 to 5 years (17,20,27–32), long-term studies after consistent radiotherapeutic approaches are still needed.

When an irradiated VS becomes symptomatic and displays continued growth, microsurgical salvage is often indicated. Unfortunately, the surgery can be complicated by scarring and increased perioperative morbidity (11,33–35). Slattery and Brackmann (33) reviewed a series of five patients with recurrent VS after stereotactic radiation. Three of five patients had complete facial palsy preoperatively, and significant scarring to the facial nerve and brainstem was encountered intraoperatively. This represented a substantially poorer outcome compared with comparably sized tumors treated primarily with microsurgical resection (1,3,4,12). The purpose of our retrospective study is to more fully clarify the clinical presentations, intraoperative findings, histopathology, and postoperative follow-up of four patients with recurrent VS after primary stereotactic radiation.

PATIENTS AND MATERIALS

Subjects used for this study received either primary gamma knife radiosurgery or FSR for VS diagnosed by gadolinium-enhanced MRI. Informed consent was obtained from all patients used in this study. In all four subjects, microsurgical salvage resection was prompted by recurrent tumor growth and associated delayed cranial neuropathies. Tumor resection was performed using a retrosigmoid craniotomy approach by a neurotologic surgeon and neurosurgeon. Intraoperative cranial nerve monitoring was used in all cases. A retrospective review of the medical records of two tertiary care medical centers was performed. Axial and coronal, gadolinium-enhanced MRI scans were analyzed and correlated with intraoperative findings and histopathology. Hematoxylin and eosin–stained pathologic slides were retrieved from the files of the respective departments of surgical pathology.

CASE REPORTS

Case 1

A healthy 72-year-old woman presented to an outside institution with progressive tinnitus and sensorineural

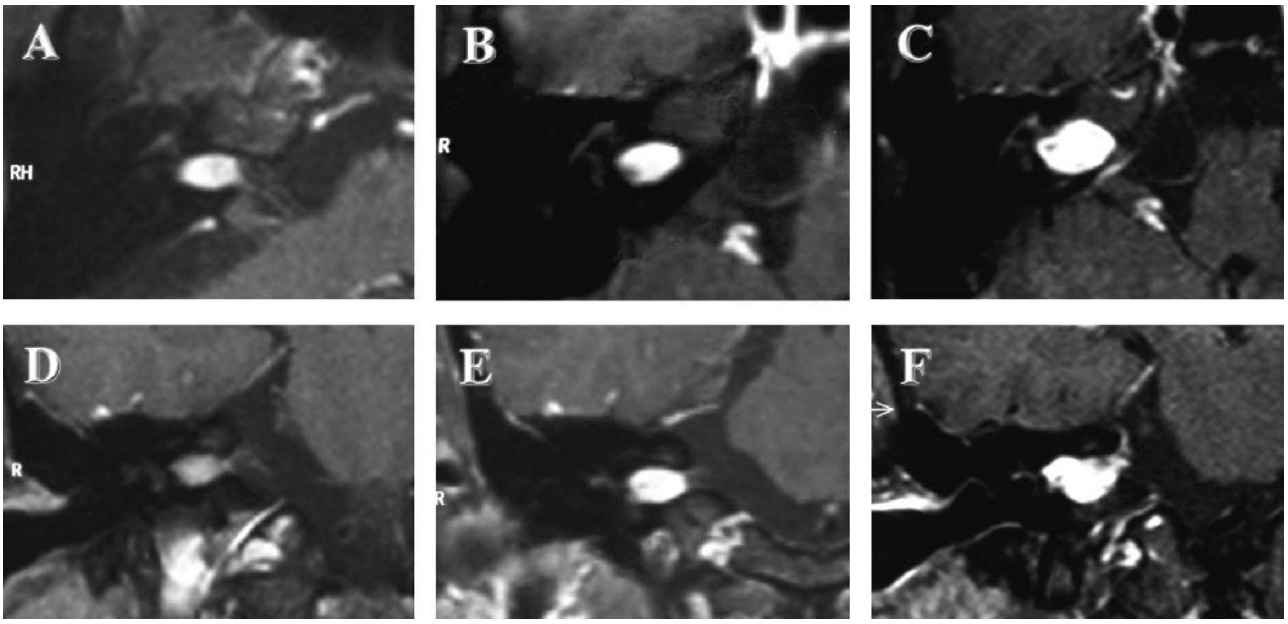

FIG. 1. T1-weighted, post–gadolinium-enhanced MRI scans of the cerebellopontine angle from Case 1. Axial images (*A–C*) and coronal sections (*D–F*). (*A* and *D*) Pre–gamma knife MRI scans demonstrating a right-sided 1.0-cm VS, with scans at 6 months (*B* and *E*) and 20 months (*C* and *F*) after radiation. Slight tumor involution seen in *B* was followed by rapid regrowth to 1.5 cm at 1 year after radiosurgery (MRI scan not shown).

hearing loss. She denied dizziness, headaches, facial nerve twitching, or weakness. A right-sided, 1.0 × 0.7-cm intracanalicular VS was diagnosed (Fig. 1), and she underwent gamma knife radiosurgery. The radiation dose delivered was 13 Gy. She initially did well, with 50% tumor involution at 6 months after radiation therapy. However, she began to experience episodic right-sided facial nerve spasms at 12 months after radiosurgery. These symptoms were partially relieved with botulinum toxin injections. Serial MRI (Fig. 1) demonstrated increased tumor growth to 1.5 × 1.0 cm after radiosurgery. She was referred for surgical management.

Intraoperative findings

A right suboccipital craniotomy approach was used. Significant scarring and fibrosis of the inferior and anterior portions of this intracanalicular tumor were encountered, with no evidence of radiation-induced changes of the posterior and medial surfaces. Complete resection of VS was achieved, with anatomic preservation of the facial nerve.

Postoperative course

She recovered uneventfully, with normal facial nerve function (Fig. 2, A–C). Her hospital stay was 5 days. Now, 15 months after surgery, she has no recurrent facial nerve spasms. Final pathologic findings were consistent with vestibular schwannoma.

Case 2

A 54-year-old healthy woman presented with unilateral sensorineural hearing loss and dizziness, and was diagnosed with a 2.6-cm left-sided acoustic neuroma. She underwent FSR to 25 Gy. A 6-month follow-up MRI

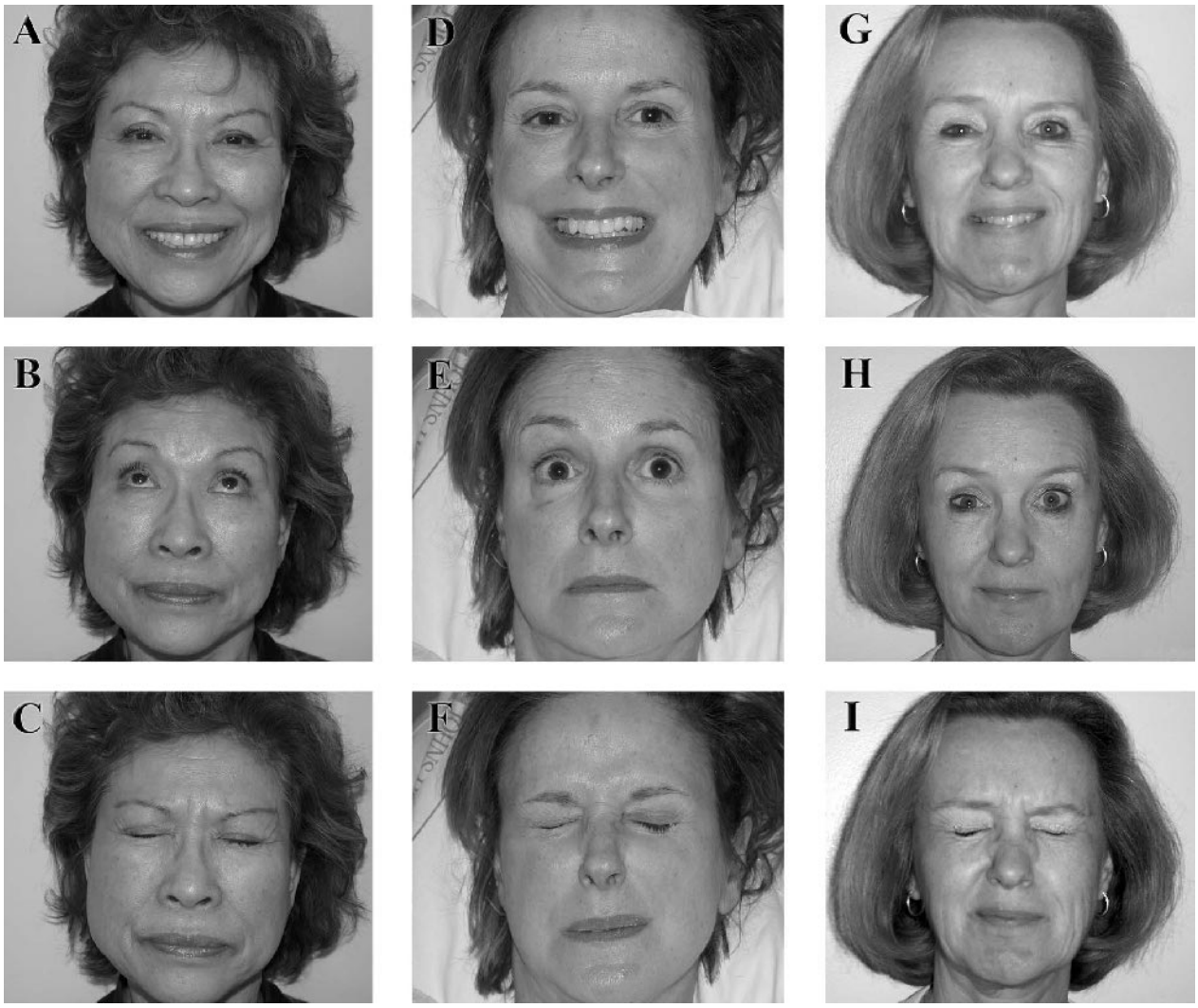

FIG. 2. Postoperative facial nerve function after microsurgical resection of recurrent irradiated VS in Case 1 (*A–C*) demonstrates House-Brackmann scale Grade I/VI facial function at 10 months after resection of a right-sided VS. (*D–F*) Slight left facial synkinesis in Case 2 seen on postoperative day 3. Her function has improved since discharge. (*G–I*) Case 3 is shown, and exhibits mild facial weakness, Grade I to II/VI, 9 months after resection of a right-sided, recurrent VS after stereotactic radiation.

scan demonstrated no tumor regrowth. Two years after completion of FSR, she began to develop progressive left-sided tongue and oral numbness. Repeat imaging studies showed a 2.9 × 2.0-cm acoustic neuroma (Fig. 3). She was referred for surgical management.

Intraoperative findings

A left suboccipital craniotomy approach was used. Scarring and fibrosis were seen involving the tentorium, arachnoid, and cerebellum. Tumor and scar extended to the brainstem and involved cranial nerves V, VII, IX, X, and XI.

Postoperative course

She developed mild mental status changes on postoperative Day 1 secondary to cerebellar edema and hydrocephalus, and responded well to high-dose intravenous steroids. Her facial nerve function was Grade I to II/VI during her hospital stay (Fig. 2, D–F). She exhibited progressive difficulty managing her secretions; flexible fiberoptic laryngoscopy and a video swallowing study demonstrated aspiration and left vocal fold paralysis. She received a Cymetra (LifeCell Corporation, Branchburg, NJ, U.S.A.) (micronized AlloDerm, LifeCell) left vocal fold medialization and percutaneous gastrostomy placement on the eighth postoperative day. She was discharged 11 days after surgery in good condition (which included 2 days of inpatient acute rehabilitation). Final pathologic findings were consistent with vestibular schwannoma.

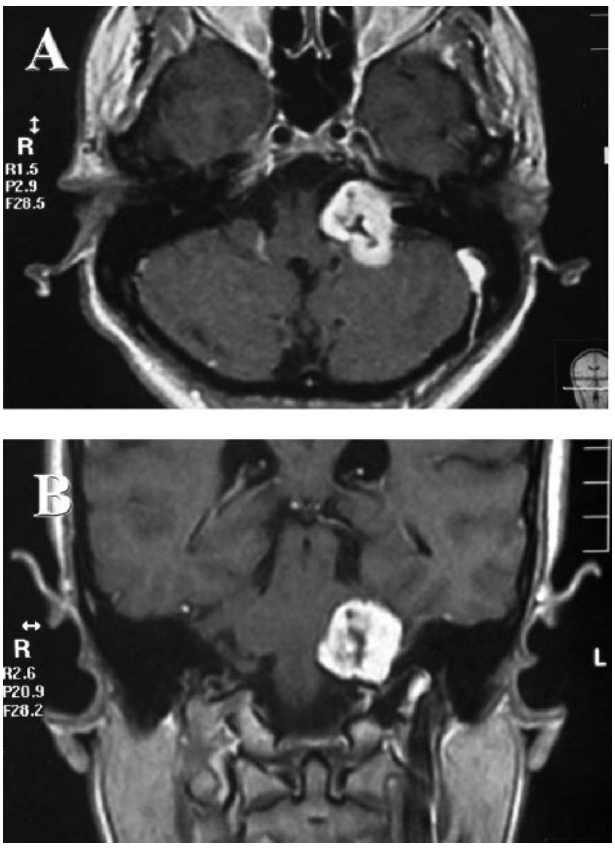

FIG. 3. T1-weighted, post–gadolinium-enhanced MRI scans of the cerebellopontine angle from Case 2. A left-sided, 2.9-cm VS with central necrosis is shown (*A*, axial; *B*, coronal), presenting 2 years after fractionated stereotactic radiotherapy for a 2.6-cm VS.

Case 3

An otherwise healthy 50-year-old woman presented to an outside institution with unilateral sensorineural hearing loss and tinnitus. Her pretreatment MRI scan showed a right-sided 1.3 × 0.8-cm VS (Fig. 4). Two months later, she underwent FSR; 25 treatments were given, for a total delivered dose of 45 Gy. An MRI scan 19 months after FSR revealed subtle tumor growth within the cerebellopontine angle (CPA) (Fig. 4). Two months later, she developed progressive ipsilateral facial spasms. Minimal tumor growth was noted on a repeat MRI scan (Fig. 4). She was referred for surgical management.

Intraoperative findings

A right suboccipital craniotomy approach was used. Dense adhesions were found along the cranial nerve IX and X complex. The porus acousticus and CPA portion of the tumor were scarred to the facial nerve. The intracanalicular tumor had no evidence of gross postradiation changes.

Postoperative course

On the first day postoperatively, she had normal facial nerve function (Grade I/VI). She developed Grade II/VI facial weakness on the second postoperative day. She was maintained on intravenous dexamethasone and was discharged on the third postoperative day on oral steroids. Fourteen months after surgery, her facial nerve outcome is Grade II/VI (Fig. 2, G–I). Final pathologic findings were consistent with vestibular schwannoma.

Case 4

A 55-year-old woman presented with asymmetric sensorineural hearing loss, tinnitus, and mild dizziness. There were no facial nerve symptoms. She was diagnosed with a left-sided, 1.3-cm VS and managed primarily with gamma knife radiosurgery. The radiation dose delivered was 14 Gy. Slight tumor involution was seen during the first year after treatment (Fig. 5). She subsequently developed facial nerve spasms and synkinesis; follow-up scans demonstrated increased tumor growth (Fig. 5). Her facial nerve symptoms, headaches, and dizziness progressed and she was referred for surgical management. A preoperative MRI scan 42 months after radiosurgery showed a 1.8 × 1.8 × 1.8-cm mass in the left CPA (Fig. 5).

Intraoperative findings

A left suboccipital craniotomy approach was used. Varying degrees of fibrosis of the tumor were seen, particularly along the anterior capsule, which was densely adherent to the facial nerve in the CPA. The tumor dissected easily in the internal auditory canal. A complete resection was performed, maintaining the integrity of the

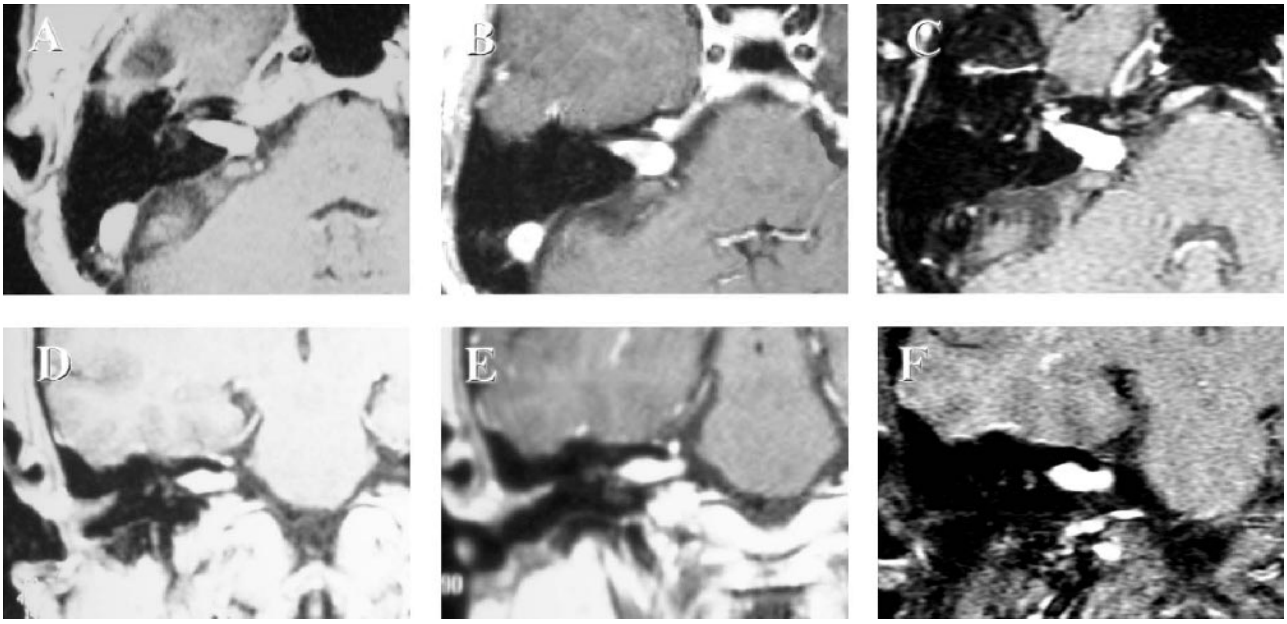

FIG. 4. T1-weighted, post–gadolinium-enhanced MRI scans of the cerebellopontine angle from Case 3 (*A–C*, axial; *D–F*, coronal) demonstrating a right-sided VS with minimal extension into the cerebellopontine angle. Interval scans before fractionated stereotactic radiotherapy (*A* and *D*), and 22 months (*B* and *E*) and 32 months (*C* and *F*) after radiation, reveal 2 to 3 mm of tumor regrowth accompanying hemifacial spasm in this patient.

facial nerve in the CPA and internal auditory canal. The facial nerve stimulated at the brainstem to 0.4 mA.

Postoperative course

She exhibited a Grade VI facial nerve palsy immediately postoperatively, and a moisture chamber was placed for eye protection. She had an uneventful hospital stay and was discharged to home on the fifth postoperative day. A gold weight was placed as an outpatient procedure to provide adequate eye closure. Final pathologic findings were consistent with vestibular schwannoma.

RESULTS

We present four patients who underwent primary gamma knife radiosurgery (2) or FSR (2) for VS and demonstrated persistent tumor VS growth. The average age at surgery was 58 years, with a mean time to recurrence of 1.6 years (range, 1–2 years) (Table 1). Tumor growth from 2 to 5 mm from the time of stereotactic radiation to microsurgical resection was observed radiographically. Three patients presented with facial neuropathies and one with trigeminal nerve symptoms after primary radiation therapy. All subjects underwent retrosigmoid craniotomy and microsurgical resection of recurrent VS. The mean follow-up postoperatively was 12 months (range, 6.0–15.3 months) (Table 1).

Intraoperative findings

Capsular fibrosis on the medial or anterior surfaces of the irradiated tumor in the CPA was evident in all four cases, consistent with previous studies demonstrating scarring of the tumor capsule (33). These changes substantially complicated microsurgical dissection to free the facial and caudal cranial nerves from the tumor surface. Although preservation of facial nerve integrity was achieved in all cases, tumor dissection was difficult, and significant facial and caudal cranial neuropathies resulted in two of four cases. Interestingly, no scarring of the intracanalicular component of the VS recurrence was encountered in three of four cases.

Radiographic findings

All patients underwent preradiation and preoperative gadolinium-enhanced MRI scanning to evaluate the CPA. Enlargement of tumor dimension was seen in these four cases, ranging from 1 to 5 mm/yr after radiotherapy (representative radiography is shown in Figs. 1 and 3–5). Both Case 1 and Case 4 exhibited the fastest growth rate as seen radiographically and, interestingly, received gamma knife radiosurgery and the lowest cumulative radiation doses at 13 and 14 Gy, respectively (Table 1).

Case 1 initially presented with asymmetric hearing loss and a right-sided, 1.0-cm, intracanalicular VS (Fig. 1, A and D). Initial tumor involution was followed by rapid tumor growth at 1 year after treatment to 1.5 cm, accompanied by hemifacial spasm. Regrowth of VS was seen with expansion of the internal auditory canal, with minimal extension into the CPA (Fig. 1, C and F). Central necrosis and cystic changes were not observed.

Case 2 presented with a larger VS, measuring 2.6 cm. After primary FSR, she experienced trigeminal hypesthesias that were associated with 3 mm of tumor growth over 1.5 years. Follow-up MRI scans approximately 2

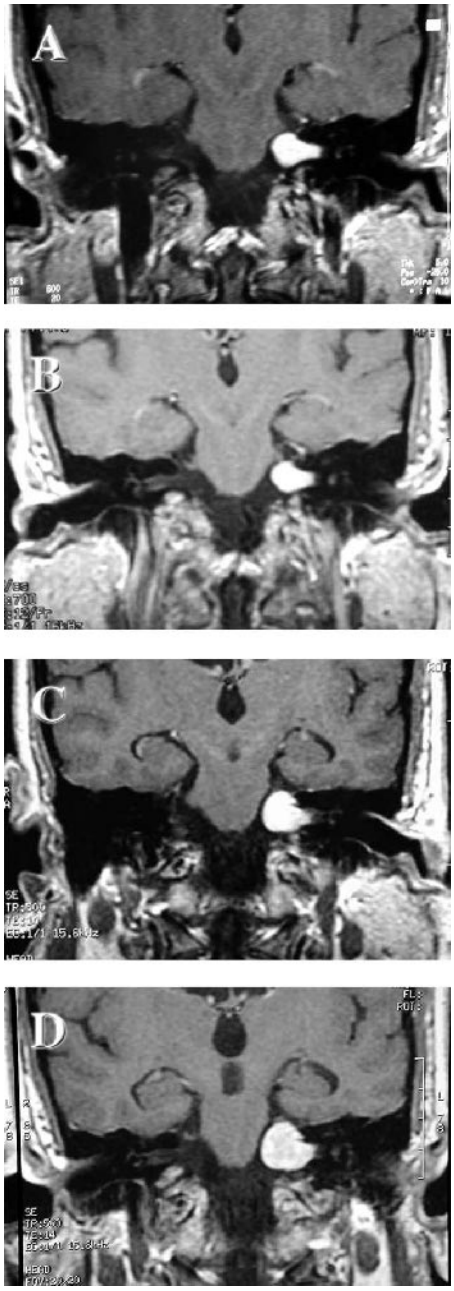

FIG. 5. T1-weighted, post–gadolinium-enhanced coronal MRI scans of the cerebellopontine angle from Case 4. A 1.3-cm left-sided VS was diagnosed before gamma knife radiosurgery (*A*). Slight tumor involution was observed initially at 1 year after radiation (*B*). (*C* and *D*) Four to 5 mm of tumor regrowth at 2 years and 3.5 years after radiosurgery, respectively. Note the decreased attenuation within the core of the tumor (*D*).

years after radiation revealed a 2.9-cm enhancing lesion in the CPA, with brainstem compression and decreased attenuation within the core of the tumor (Fig. 3). Loss of central enhancement presumably correlates with necrosis, whereas any return of enhancement associated with tumor shrinkage represents scar and fibrosis formation (20). These changes noted radiographically were associated with a variable degree of scarring and fibrosis to the facial nerve and the lower cranial nerves encountered intraoperatively.

Case 3 also presented with unilateral sensorineural hearing loss and was found to have a right-sided, 1.3-cm, enhancing lesion of the internal auditory canal and CPA (Fig. 4, A and D). Subtle tumor growth of 1 mm was seen approximately 2 years after FSR, with no evidence of central necrosis or involution (Fig. 4, B and E). One to 2 mm of additional growth into the CPA was observed at 3 years after radiation, accompanying hemifacial spasm (Fig. 4, C and F).

Case 4 presented with unilateral sensorineural hearing loss and was found to have a 1.3-cm left-sided VS involving the internal auditory canal and CPA, with minimal brainstem involvement (Fig. 5A). Coronal MRI scans 1 year after gamma knife revealed tumor shrinkage (Fig. 5B). At 1.5 years after surgery, 2 to 3 mm of tumor regrowth and increased brainstem compression were seen (Fig. 5C), associated with facial synkinesis, headaches, and increased dizziness. Preoperative MRI 3.5 years after radiosurgery demonstrated a 1.8 × 1.8-cm VS with brainstem indentation (Fig. 5D).

Histopathologic findings

By light microscopy, these four irradiated tumors showed features of typical VS (Fig. 6). The dominant component in each specimen was that of elongated bipolar cells disposed in fascicles (Antoni A pattern). Less compact areas with xanthoma cells and small round tumor cells (Antoni B pattern) constituted a minor component of these tumors.

All four irradiated VSs were moderately cellular. The tumors showed varying degrees of nuclear pleomorphism with hyperchromasia and vascular hyalinization with surrounding hemosiderin deposition (Fig. 7). It should be emphasized that these degenerative changes are common in nonirradiated VS. They do not necessarily reflect alterations secondary to radiation therapy. None of these VSs treated primarily with stereotactic radiation exhibited necrosis, zones of scar proliferation, or any evidence of malignant transformation.

DISCUSSION

The absence of histopathologic alterations attributable to radiation in this small series of irradiated VS is consistent with previous findings (24). The lack of significant degenerative tumor changes can be explained by 1) global tumor radiation resistance, 2) radiation resistance in a subpopulation of tumor cells followed by expansion of the resistant clones, or 3) insufficient radiation dosage delivered to all or part of the tumor. Other studies describing the histopathologic features of VS after gamma knife radiosurgery have noted varying degrees of treatment-related changes (Table 2). In a series of two irradiated VS, Hirato et al. (36) described partial tumor necrosis, fibrosis, and vascular changes after gamma knife radiosurgery (Table 2). They concluded that such

TABLE 1. *A review of irradiated vestibular schwannoma histology*

Authors	Age (y)	Sec	Radiation modality	Radiation dose	Time to recurrence/ surgery	Histopathologic changes
Slattery and Brackmann, 1995 (33)	39	Female	Gamma knife radiosurgery	N/A	11 yr	Tumor cells and alterations consistent with VS, degenerative changes, hyalinization, and thickening of vessel walls
Slattery and Brackmann, 1995 (33)	65	Female	Gamma knife radiosurgery	N/A	6 mo	Viable tumor cells with degeneration, consistent with VS
Slattery and Brackmann, 1995 (33)	24	Male	Stereotactic gamma irradiation	N/A	6 mo	Viable tumor cells consistent with VS (Hx of NF-2)
Slattery and Brackmann, 1995 (33)	18	Female	Stereotactic proton irradiation	N/A	11 mo	Tumor cells consistent with VS (Hx of NF-2)
Slattery and Brackmann, 1995 (33)	39	Male	Gamma knife radiosurgery	N/A	2 yr	Tumor cells consistent with VS
Hirato et al., 1996 (27)	51	Female	Gamma knife radiosurgery	17 Gy margin, 34 Gy central	5 mo	Parenchymal necrosis and fibrosis centrally, vascular and endothelial proliferation peripherally, tumor cells consistent with VS
Hirato et al., 1996 (27)	58	Male	Gamma knife radiosurgery	12 Gy margin, 24 Gy central	4 mo	Central necrosis surrounded by residual tumor cells consistent with VS, pericytic proliferation of the vascular wall
Fukuoka et al., 1998 (36a)	25	Female	Gamma knife radiosurgery	9 Gy margin, 22.5 Gy central	5 mo	Tumor cells with condensed rounded-shaped nuclei, intimal thickening of blood vessel with surrounding necrosis, consistent with VS
Fukuoka et al., 1998 (36a)	48	Female	Gamma knife radiosurgery	12 Gy margin, 24 Gy maximum dose	18+ mo	Tumor cells consistent with VS
Kwon et al., 1999 (24)	64	Female	Gamma knife radiosurgey	12 Gy margin	10 mo	Tumor cells and alterations consistent with VS, no necrosis or vascular proliferation
Kwon et al., 1999 (24)	35	Male	Gamma knife radiosurgery	14 Gy margin	64 mo	Tumor cells and alterations consistent with VS, no necrosis or vascular proliferation
Kwon et al., 1999 (24)	39	Male	Gamma knife radiosurgery	13 Gy margin	5 mo	Tumor cells and alterations consistent with VS, no necrosis or vascular proliferation
Kwon et al., 1999 (24)	37	Female	Gamma knife radiosurgery	12 Gy margin	34 mo	Tumor cells and alterations consistent with VS, no necrosis or vascular proliferation

VS, vestibular schwannoma; Hx, history.

changes contributed to tumor growth suppression, at least in the short term (36). Kwon et al. (24), in contrast, could not identify any histologic alterations that could be directly attributed to radiation effect in their four cases of VS treated with gamma knife radiosurgery. Specifically, the tumors were not necrotic, and the vascular changes noted in the tumor recurrences were also noted in the same tumors before radiosurgery. Similarly, Slattery and Brackmann (33) could not identify any radiation-induced histologic alterations in their group of five recurrent VSs managed with stereotactic radiation (Table 2).

However, the clinical and surgical findings after radiation in these four patients were fairly uniform. Cranial neuropathies developed after radiation therapy in all four

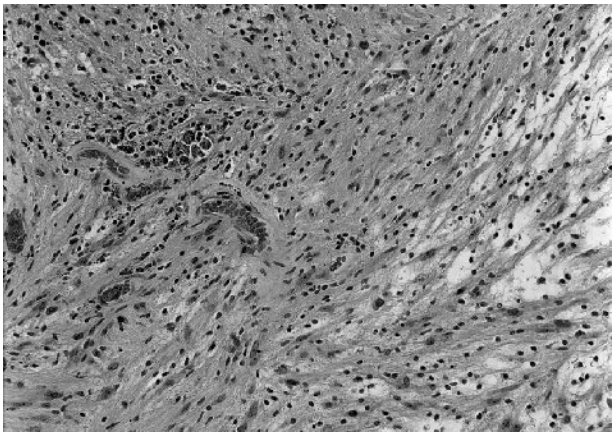

FIG. 6. Vestibular schwannoma from Case 1 after gamma knife radiosurgery. Cellular areas of spindled tumor cells (i.e., Antoni A areas, *left*) are interrupted by less cellular zones containing foamy histiocytes (i.e., Antoni B areas, *right*) (hematoxylin and eosin; original magnification, ×100).

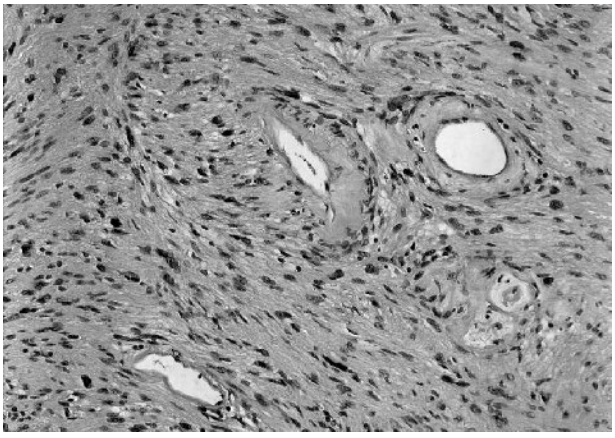

FIG. 7. Vestibular schwannoma from Case 3 after stereotactic radiotherapy. This representative section reveals perivascular hyalinization and spindled tumor cells with enlarged hyperchromatic nuclei, consistent with classic VS histology (hematoxylin and eosin; original magnification, ×100).

TABLE 2. *Patient demographics*

Patient	Sex	Diagnosis	Primary radiation modality	Radiation dose (Gy)	Size of tumor before radiation (largest dimension) (cm)	Size of tumor preoperatively (largest dimension) (cm)	Age at surgery (yr)	Time to tumor regrowth (yr)	Preoperative symptoms	Facial nerve function postoperatively[a]	Postoperative follow-up (mo)
Case 1	Female	Vestibular schwannoma	Gamma knife radiosurgery	13	1.0	1.5	72.5	1	Hemifacial spasm	I/VI	10.3
Case 2	Female	Vestibular schwannoma	Fractionated sterotactic radiosurgery	25	2.6	2.9	55.4	2	Trigeminal nerve paresthesia	I–II/VI	1.0
Case 3	Female	Vestibular schwannoma	Fractionated stereotactic radiosurgery	45	1.3	1.5	50.4	2	Hemifacial spasm	I–II/VI	9.2
Case 4	Female	Vestibular schwannoma	Gamma knife radiosurgery	14	1.3	1.8	55.6	1.5	Hemifacial spasm	VI/VI	1.5

[a]House-Brackmann scale.

cases, accompanied later by continued tumor growth. Varying degrees of fibrosis were encountered intraoperatively, complicating dissection. Significant scarring after radiation was usually observed in the CPA, without evidence of fibrosis within the internal auditory canal in three of four cases. Despite these changes, anatomic preservation of the facial nerve was successful in all four cases, with three of four exhibiting normal or near normal facial nerve function 1 to 10 months after surgery. Unfortunately, the dense adhesions involving the CPA in Case 2 resulted in lower cranial nerve palsies after surgical salvage and required vocal cord rehabilitation and an enteral feeding tube.

Although our findings support previously published reports that show an increased risk of delayed cranial neuropathies and surgical complications after stereotactic radiation, an increasing number of patients are undergoing gamma knife radiosurgery or FSR for VS. Indeed, recently published series of patients undergoing primary radiation treatment of VS have shown promising outcomes regarding tumor control rates, hearing preservation, facial nerve function, and posttreatment complications. Risks inherent with an open surgical procedure and general anesthesia are avoided. However, many of these studies do not have consistent treatment protocols, earlier series with longer follow-up periods used higher radiation doses, and debate now exists within the stereotactic radiation literature regarding the relative efficacy of gamma knife radiosurgery compared with FSR (16). Also, radiation therapy is often used for smaller VSs, with microsurgical resection reserved for larger tumors. A comparison of outcomes regarding complication rates is difficult to accurately assess unless carefully designed studies are performed to control for radiation technique, total dose administered, and tumor size.

Kondziolka et al. (18) evaluated 162 patients who underwent gamma knife radiosurgery for sporadic VS. Although the overall tumor control rate was 98%, only 60% of these patients received follow-up imaging studies beyond 5 years (18, 37). In addition, the initial dose delivered to the tumor margin was reduced from 18 to 20 Gy to 14 to 16 Gy to reduce the complication rate, making it difficult to interpret the tumor recurrence rate for those patients treated later in the study. In fact, 72% of these patients received the higher dosage (18, 37). In addition, VS is a slow-growing tumor with a low proliferative index; studies have shown that 26 to 86% of VSs show little or no growth for many years (38). When tumor growth before radiosurgery is stable or very slow, it is difficult to assess whether no growth after radiation therapy is a measure of treatment efficacy or merely a reflection of the natural course of the lesion (39). Clearly, long-term outcome analyses of patients receiving 14 to 16 Gy will be crucial in determining tumor control rates using lower dose schedules.

The underlying mechanisms leading to changes in VS growth potential after stereotactic radiation are not completely understood. Studies at the Karolinska Institute evaluated the dose-response relationships of irradiated acoustic neuroma in tissue culture. Although death occurred in some cells with a single 30-Gy dose via a cobalt-60 gamma radiation source, a number of cells survived, even after doses of 150 Gy (40). The wide range of radiosensitivity in VS may be related to an inherently low proliferative index. If only a small percentage of cells within a given VS is dividing, the bulk of the tumor remains relatively radioresistant, especially to low doses of radiation (16). Additional studies using molecular and genetic markers may reveal the underlying mechanisms leading to radiation resistance in irradiated VS.

Within the limits of this small series of irradiated VS with brief clinical follow-up, we did not observe histologic changes such as cellular atypia suggestive of malignant degeneration. Nevertheless, the long-term theoretic risk of second tumor formation after stereotactic radiation must be considered. Both low- and high-dose radiation therapy have been shown to increase the risk of developing neoplasms of the central nervous system. An association between low-dose radiation therapy in childhood and the risk of benign and malignant intracranial neoplasms has been demonstrated in previous studies, with latency periods of 16 to 30 years (41–48). A study

TABLE 3. *Review of malignancies associated with stereotactic radiation for vestibular schwannoma*

Authors	Diagnosis before radiation	Age (yr)	Sex	Location	Initial management	Radiation method	Radiation dose	Time to recurrence or new growth	Diagnosis at surgery
Shamisa et al., 2001 (41)	Vestibular schwannoma[a]	57	Female	Cerebellopontine angle	Radiation	Gamma knife radiosurgery	17.1 Gy average dose (27.5 Gy central, 11 Gy margin)	First surgery, 8 mo after radiosurgery Second surgery, 7.5 yr after radiosurgery	First surgery, vestibular schwannoma Second surgery, glioblastoma multiforme
Comey et al., 1998 (35)	Vestibular schwannoma[a]	44	Male	Cerebellopontine angle	Radiation	Gamma knife radiosurgery	14.36 Gy margin, 34 Gy maximum	5 yr	Malignant schwannoma triton tumor[b]
Kurita et al., 1997 (51)	Vestibular schwannoma[a]	N/A	N/A	Cerebellopontine angle	Radiation	Gamma knife radiosurgery	N/A	6 yr	Malignant schwannoma
Noren, 1997 (51a)[h]	Vestibular schwannoma[a]	18	N/A	Cerebellopontine angle	Radiation	Gamma knife radiosurgery	N/A	6 yr	Malignant schwannoma
Hanabusa et al., 2001 (50)	Vestibular schwannoma[c]	57	Female	Cerebellopontine angle	Surgery	Gamma knife radiosurgery (after first surgery)	15 Gy margin, 30 Gy maximum core dose	Recurrence after first surgery, 4 yr Recurrence after radiosurgery, 6 mo	Second surgery, malignant schwannoma[d]
Thomsen et al., 2000 (49)	Vestibular schwannoma[a,f]	19	Female	Cerebellopontine angle	Radiation	Stereotactic radiotherapy	12 Gy margin, 20 Gy maximum	6 yr	Meningosarcoma[g]

[a]Diagnosed radiographically.
[b]Patient died 1 yr after new symptoms with intracranial dissemination.
[c]Diagnosis made at autopsy.
[d]Diagnosed at first surgery.
[e]Patient died 6.5 yr after initial treatment.
[f]Neurofibromatosis Type 2.
[g]Patient died 8 yr after the initial diagnosis.
[h]Comey et al., personal communication, 1997.

from Israel correlated the late development of intracranial neoplasms with low-dose radiation therapy (average, 1.5 Gy) for childhood tinea capitis (46). Analysis of 10,834 patients with brain and nervous system tumors compared with 10,834 matched controls and 5,392 nonirradiated siblings revealed a relative risk of 8.4 for developing a neural tumor of the head and neck after low-dose radiation in childhood (46). The risk of neoplastic transformation was greatest 15 to 24 years after irradiation. Finally, although published cases are rare, there are several reports of radiation therapy–associated malignancies in the CPA (35,41,49–51) (Table 3). Cahan et al. (52) proposed criteria for radiation-induced malignancies: 1) a second tumor must be located within the irradiated bed; 2) a period of time must have elapsed between radiotherapy and growth of the second tumor; 3) the histology of the second tumor must be distinct from the initial tumor; and 4) the patient must not have any preexisting condition or genetic predisposition for malignancy formation. Accordingly, there are two cases, as shown in Table 3, that fulfill the Cahan criteria for a radiation-induced malignancy. Several other reports of malignant transformation after radiosurgery for benign intracranial neoplasms have been reported (53–58). Table 3 summarizes the reported cases of either malignant schwannoma, glioblastoma multiforme, or meningosarcoma that have been associated with stereotactic radiosurgery or FSR for VS. Comey et al. (35) argue that the malignant schwannomas seen in three cases were most likely present before radiation therapy. However, Hanabusa et al. (50) present a compelling case of a VS diagnosed before gamma knife surgery. This lesion demonstrated regrowth after single-shot radiosurgery to 15 Gy (30 Gy maximum dose) and, on reoperation, the recurrent tumor was found to be malignant (50). This patient died 6.5 years after her initial therapy. It is interesting to note that Hanabusa et al. favored spontaneous malignant degeneration as the most likely cause of this patient's demise. Malignant schwannomas are certainly rare, with only seven reported in the literature. However, four of these cases have been associated with radiation therapy. Studies using long-term radiographic and clinical follow-up 10 to 20 years after radiation therapy for VS are imperative to assess true rates of recurrence and the possible risk for second tumor formation. Finally, histologic and molecular analysis of additional VSs treated primarily with radiation will provide greater insight into the mechanisms of tumor growth suppression or regrowth after gamma knife radiosurgery or FSR.

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INVITED COMMENT

The authors present four case reports of patients with microsurgical excision of vestibular schwannomas following primary radiation therapy. The authors provide an excellent review of previously published reports examining this topic. The long-term effects of stereotactic radiation surgery are yet to be determined and will require further study.

Additional studies are necessary to determine why some tumors do not grow after diagnosis and others do grow. The exact mechanism of radiosurgery is also currently not understood with respect to vestibular schwannomas. These areas require additional research. This article will help future investigators as they try to understand the best treatment option for vestibular schwannomas.

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