Malignant Transformation of a Vestibular Schwannoma After Gamma Knife Radiosurgery

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OBJECTIVE: To report a single case of malignant transformation of a vestibular schwannoma after radiosurgery and review the growing body of literature describing patients with malignant transformation of primary benign tumors after radiosurgery, including vestibular schwannoma.

METHODS: A 46-year-old woman presented with right facial paresthesias and imaging consistent with a right-sided vestibular schwannoma (volume approximately 18.5 cm³).

RESULTS: The patient underwent subtotal resection followed by Gamma Knife radiosurgery (GKRS) 6 months after surgery. Initial histology showed a benign vestibular schwannoma with an MIB-1 labeling index of 5.7%. At 43 months after GKRS, the patient underwent repeat subtotal resection of a benign vestibular schwannoma (MIB-1 labeling index 7.4%). At 59 months after GKRS, she underwent a third resection, and histology showed frank malignant transformation (MIB-1 labeling index 33.8%).

CONCLUSIONS: Malignant vestibular nerve tumors are extremely rare; only 18 cases have been reported in the literature. Our patient is the sixth pathologically confirmed case of malignant transformation after radiosurgery, supporting the contention that radiosurgery itself may play a causative role in transformation. In a histologically benign lesion, the presence of an elevated MIB-1 labeling index may predispose toward malignant transformation in the setting of adjuvant radiosurgery.

INTRODUCTION

Nearly 200,000 benign intracranial tumors have been treated with Gamma Knife radiosurgery (GKRS) since its introduction in 1991; approximately 9% of these tumors are vestibular schwannomas (4). External-beam radiation therapy has an established theoretical advantage, reports of cases of secondary malignancy and malignant transformation of benign tumors after radiosurgery are increasing. We report the sixth case of pathologically confirmed malignant transformation in a patient who underwent GKRS after surgical resection of a vestibular schwannoma.

CASE REPORT

History and Examination

In July 2004, a previously healthy, 46-year-old woman sought treatment at the outpatient clinic of the senior author (R.W.P.) after experiencing right-sided face and tongue numbness and episodic right facial pain for 5 months. On initial physical examination, she was found to have decreased sensation on the right side of her face from V1-V3, an absent right corneal reflex, House-Brackmann (HB) grade 2 right facial palsy, and decreased hearing in the right ear. She had no personal or family history of neurofibromatosis (NF) and no stigmata of NF.

Initial Imaging

Magnetic resonance imaging (MRI) of the brain showed a right-sided, 2.65 cm × 2.38 cm × 2.94 cm (volume approximately 18.5 cm³), contrast-enhancing mass in the cerebellopontine angle with extension into the proximal internal auditory canal. An enhancing dural tail was not seen (Figure 1). These findings were consistent with a vestibular schwannoma.

Clinical Course

The patient underwent a right retrosigmoid craniectomy for resection of the cerebellopontine angle lesion. Intraoperatively, the tumor was found to be arising from the superior vestibular division of the auditory nerve. The tumor also enveloped the facial nerve and was adherent to the brainstem. Subtotal resection (STR) was achieved (Figure 1); residual tumor remained on the vestibular nerve and brainstem. The patient was treated with a lumbar drain.
Pathologic analysis was consistent with benign schwannoma. No mitotic figures, significant atypia, or necrosis was seen. The MIB-1 labeling index was 5.7% (Figure 2).

Postoperatively, the patient was noted to have new slurred speech, decreased gag reflex, and deviation of the uvula to the right. She was diagnosed with right vocal cord paralysis and was treated with injection of absorbable gelatin sponge (Gelfoam) in the right vocal fold. She was discharged to a rehabilitation facility with a feeding tube, continued decreased sensation on the right side of her face, HB grade 2 facial palsy, no functional hearing in the right ear, and improving phonation.

The patient did well in rehabilitation and was examined in the senior author’s clinic in January 2005. The right facial palsy was absent, the uvula was midline, and right face sensation had returned. However, she continued to have right vocal cord paralysis and had complete loss of sensorineural hearing on the right. Compared with immediate postoperative MRI, slight enhancement was visible at the cerebellopontine angle, suggestive of tumor regrowth (Figure 1). Later that month, she underwent GKRS of the residual tumor. She received 14 Gy at the 50% isodose line encompassing 98% of the tumor at a volume of 3.9 cm³. She experienced no complications related to the procedure.

The patient was followed with serial brain MRI, and initially the residual tumor remained stable. In June 2008, routine follow-up MRI showed a significant tumor recurrence associated with brainstem compression (Figure 1). Although her symptoms had not progressed, the patient underwent repeat right retrosigmoid craniotomy for resection of the presumed recurrence in August 2008. STR (90%) was achieved. Residual tumor remained on the proximal vestibular nerve and brainstem. Postoperative MRI showed a thin rim of enhancing tumor along the resection margin (Figure 1). After surgery, the patient had an HB grade 2 right facial palsy but was otherwise at her neurologic baseline. She did well and was discharged home. Pathologic analysis was consistent with benign schwannoma but with degenerative changes, possibly reflecting prior surgery or the effect of radiation treatment. No mitotic figures or necrosis was seen.

Figure 1. Representative preoperative and postoperative axial T1-weighted magnetic resonance imaging (MRI) with contrast enhancement shown at multiple time points. (A) Preoperative MRI for the July 2004 resection shows a predominantly cisternal tumor, with extension into the proximal internal auditory canal. (B) Immediate postoperative MRI shows central debulking with decompression of the brainstem. (C) In January 2005, the patient underwent Gamma Knife radiosurgery of the residual tumor, which had shown some regrowth. (D) In June 2008, the patient underwent resection for a significant recurrence with brainstem compression. (E) Only a thin rim of tumor was left on the cerebellar peduncle and lateral brainstem. The facial nerve was spared. (Used with permission from the Barrow Neurological Institute.)
Mild atypia was noted. The MIB-1 labeling index was 7.4%.

In December 2009, the patient returned to the clinic complaining of 1 week of increasing dizziness, gait disturbance, and headache. On physical examination, she was noted to have persistent HB grade 2 facial palsy, with new slurred speech, right abducens palsy, and right tongue deviation. MRI showed a 3.4 cm × 3.6 cm × 2.9 cm mass (volume approximately 34.9 cm³) in the resection bed with both cystic and solid components associated with significant brainstem compression (Figure 3).

She was taken to the operating room on an urgent basis and underwent a right translabyrinthine craniectomy for resection of the recurrence. Intraoperatively, the tumor extensively involved the trigeminal and facial nerves. Analysis of frozen sections showed malignant features, and both cranial nerves were sacrificed. The tumor had also infiltrated the brainstem. Gross total resection (GTR) was achieved.

Postoperative MRI confirmed GTR with no residual enhancement (Figure 3). After surgery, the patient had an HB grade 6 right facial palsy, right facial numbness, right abducens palsy, decreased gag reflex, and right tongue deviation. She did well and was discharged to a rehabilitation facility with a feeding tube. At this time, pathology showed a markedly hypercellular spindle cell neoplasm consisting of atypical cells arranged in sheets. Mitotic figures were common. Microfoci of necrosis were evident. Findings were most consistent with a malignant peripheral nerve sheath tumor (MPNST). The overall MIB-1 labeling index was 33.8% (Figure 4).

The patient developed a pseudomeningocele, and a lumbo-peritoneal shunt was placed in January 2010. By July 2010, she had developed a large extradural recurrence with nodularity underlying her incision. In August 2010, she underwent extradural debulking. The pathology was again consistent with MPNST. Within 1 month, the patient developed increasing dysphagia, lethargy, and left hemiparesis. MRI showed profound recurrence with brainstem compression (Figure 3). She underwent a final palliative debulking via a retrosigmoid approach. After surgery, she underwent a course of palliative chemotherapy, including doxorubicin and ifosfamide, with little clinical benefit. She elected to have hospice care and died in November 2010.

**DISCUSSION**

The goals for treatment of vestibular schwannomas include long-term tumor control with preservation of facial, vestibulocochlear, and trigeminal nerve function. In particular, GTR of large vestibular schwannomas (>20 mm × 30 mm) (12, 35) is often associated with a significant risk of facial nerve injury (13% for large vestibular schwannomas, 6% for small vestibular schwannomas) (36) and hearing impairment (38% for large vestibular schwannomas, 14% for small vestibular schwannomas) (34). In such cases, STR is more tenable than pursuing complete resection.

The precise management for subtotally resected vestibular schwannomas is controversial. Two recent case series (13, 20) of 22 patients with large vestibular schwannomas (diameter 30–58 mm) showed that radiosurgery can be complementary to microsurgical resection. These patients underwent STR (between 33% and 64% by volume), and residual tumor was treated with radiosurgery (10–14 Gy at the 50% isodose line). In most patients (85%–90%), preservation of facial nerve function was excellent, suggesting that this combined modality approach has substantial merit. Nonetheless, radiosurgery is not without risk, and the risk of radiation-induced malignancy should be carefully considered as the number of patients undergoing radiosurgery increases.

Radiation oncogenesis has been a topic of active investigation for almost a century (32). Cahan and Woodard (8) defined the following five criteria by which a tumor could be considered radiation-induced:

- There is a latency between the delivery of the radiation and the development of the tumor.
- The tumor arises in the irradiated region.
- The tumor is histologically distinct from the original irradiated tumor.
- Imaging indicates that the tumor in question was not present before radiation delivery.
- The patient has no genetic predisposition to cancer.

Studies have placed the risk of developing a radiation-induced tumor after central nervous system fractionated radiotherapy between 1% and 3% (1, 33, 45). The highly targeted delivery of radiation in radiosurgery was intended to minimize the risk of radiation oncogenesis. However, radiosurgery-associated tumors, including meningiomas (25, 39), schwannomas (25), and malignant gliomas (5, 21, 27, 38, 52), have been reported. One difficulty in showing the causality of radiosurgery in these cases is the lack of pathology studies before radiosurgery. This absence makes the evaluation of the tumor by the criteria of Cahan and Woodard (8) impossible.

Minimizing the radiation dose is a strategy that has been used to potentially mini-
mize the risk of secondary malignancies. Historically, radiosurgical doses for vestibular schwannomas (<3 cm maximum dimension) were 17 Gy at the 50% isodose line (19). In more recent case series, doses of 12–14 Gy at the 50% isodose line were associated with good long-term tumor control (30). The impact of this dose reduction on the risk of secondary malignancy remains to be determined.

The precise mechanisms by which radiation may induce malignancy are unclear. There has been substantive speculation about radiation-induced genomic instability (2, 41, 48), although no studies have definitively shown this instability in human cancers. One case report showed the mutation of the p53 tumor suppressor gene in a malignantly transformed vestibular schwannoma (40), with no such mutation present in the initial benign vestibular schwannoma.

Evaluating the cause of malignant transformation of a benign tumor is made more challenging by the fact that malignant transformation is part of the natural history of a small proportion of benign tumors, including about 0.14% of vestibular schwannomas not associated with NF-2 (22). To our knowledge, 18 cases of malignant vestibular nerve tumors (3, 6, 10, 11, 16-19, 23, 26, 28, 29, 37, 40, 42, 44, 46, 49), including malignant vestibular schwannomas, MPNSTs, malignant triton tumors, and sarcomas (Table 1), have been reported. Malignant vestibular schwannomas and MPNSTs of the vestibulocochlear nerve are pathologically equivalent and distinct from malignant triton tumors, which show both malignant rhabdomyoblasts and malignant schwannoma cells. Malignant vestibular schwannomas and MPNSTs can have features of histopathologic sarcomas. Of these 18 reported cases, 7 were primary malignant vestibular nerve tumors (6, 16-18, 23, 26, 29), and the remaining 11 were uncertain or showed transformation from benign vestibular schwannomas (3, 10, 11, 19, 28, 37, 40, 42, 44, 46, 49).

Of the 11 patients with presumed transformation, 9 had radiosurgery as part of their treatment. However, only five of the patients had histology before radiosurgery that definitively showed a benign vestibular schwannoma (11, 19, 40, 46, 49). The significance of the distinction between primary malignant vestibular nerve tumors and

Figure 3. Representative preoperative and postoperative axial T1-weighted magnetic resonance imaging (MRI) with contrast enhancement at multiple time points. (A) Preoperative MRI for the December 2009 resection shows the dramatic recurrence with cystic change, significant brainstem compression, and surrounding edema. Intraoperative frozen-section pathology suggested malignant transformation, and aggressive resection was performed. (B) Immediate postoperative MRI shows gross total resection with no residual enhancement. (C and D) In late August 2010, now lethargic and hemiparetic, the patient underwent final palliative resection of a rapid recurrence. (E) T1-weighted MRI with contrast sequence. (D) Fluid attenuation inversion recovery sequence. (E) Despite the significant resection, the patient died in November 2010. (Used with permission from the Barrow Neurological Institute.)
transformed vestibular nerve tumors is uncertain. From one perspective, primary malignant vestibular nerve tumors are simply transformed vestibular schwannomas discovered late in the natural history. Histopathologic distinction requires that tumor progression be both preceded and followed by biopsy or resection. Histologically, malignant vestibular nerve tumors fulfill at least one of two criteria: (i) multiple mitoses per-high-powered field and (ii) invasion into nontumoral tissue (47). Malignant vestibular nerve tumors are associated with NF-2; however, outside the vestibular nerve, MPNSTs are more often seen in conjunction with NF-1 (17).

Our case definitely involved the transformation of a benign vestibular schwannoma after STR and radiosurgery, as confirmed by multiple histopathologic analyses. In the five previously reported cases, the natural history and management of the malignant vestibular schwannoma (19, 49) or MPNST (11, 40, 46) differed significantly. In the first case (19), the authors reported GTR of a benign vestibular schwannoma in a 57-year-old woman. GKRS (15 Gy at the 50% isodose line) was used 48 months after the initial operation to treat recurrent tumor. Further tumor growth 6 months after radiosurgery prompted microsurgical resection, which revealed malignant transformation. In this case, it is uncertain whether transformation occurred before or after radiosurgery. The second case was a 26-year-old woman in whom STR was achieved followed by GKRS (17 Gy at the 50% isodose line) to the residual tumor on postoperative day 30. Regrowth occurred 72 months after treatment and showed definitive malignant transformation on histology (40). In the third case, a 53-year-old man underwent GTR of a benign vestibular schwannoma followed by GKRS at an unknown time for recurrence. Symptomatic recurrence 84 months after the initial surgery prompted repeat resection, which showed MPNST (46). In the fourth case (11), malignant recurrence occurred in a 27-year-old Asian man 96 months after a second round of microsurgical debulking and immediate adjuvant GKRS (15 Gy at the 50% isodose line). The final case was a 74-year-old man who underwent GKRS (12.5 Gy at the 80% isodose line) 96 months after GTR of a benign vestibular schwannoma. Malignant recurrence was identified 156 months after his initial surgery (49).

The latency for malignant transformation appears to be on the order of years. The observed variability (54–156 months) is likely related to time of symptom onset, degree of initial debulking, and timing of repeat intervention. Our patient presented with malignant transformation 64 months after her initial surgery and 59 months after radiosurgery. Compared with the limited literature, this latency was relatively brief.

The initial histology in our patient showed an MIB-1 labeling index of 5.7%, which is elevated for a benign vestibular schwannoma (normal range, ≤4%) (50). We speculate that this elevated index reflected an increased predisposition for malignant transformation. Only one of the five previous case reports of malignant transformation after GKRS reported the mitotic index in the benign vestibular schwannoma (46). Consequently, such a correlation cannot be established. More recent studies suggest that an elevated MIB-1 index is associated with a greater probability of tumor regrowth after resection (14, 43, 50), and multiple studies have suggested that higher grade vestibular schwannomas are associated with higher mitotic indices (24, 31).

Of the 11 cases of transformation, two represent pathologically proven transformation of benign vestibular schwannomas in the absence of both radiation and NF (NF-1 or NF-2) (28, 42). The latency periods for transformation were significantly shorter than the periods observed for cases involving adjuvant GKRS—2 months (28) and 12 months (42). In a case reported by McLean et al. (28), primary resection pathology showed a benign vestibular schwannoma, but signs of malignant degeneration were present in a small portion of the tumor, perhaps accounting for the rapid malignant recurrence.

In the absence of ionizing radiation, electrocautery itself has been proposed as an agent of DNA damage and carcinogenesis. Electrocautery smoke is produced as a byproduct of thermal vessel coagulation and tissue dissection. It is known to contain low levels of group I carcinogens, including benzene, hydrogen cyanide, formaldehyde, 1,3-butadiene, and acrylonitrile (9). In vitro studies of electrocautery by-products of benign breast tissue dissection have shown mutagenic potential in Salmonella species (15). Although it is plausible that electrocautery techniques may contribute to the malignant transformation of benign lesions, the infrequency of this event in light of the global use of surgical electrocautery does not support a significant role for this mechanism. Regardless of etiology, the two aforementioned cases illustrate that malignant transformation does occur in the absence of radiation and genetic predisposition.

Radiation may not have played a causative role in our case or in the previous pathologically confirmed cases of malignant transformation after GKRS. The apparent association of radiosurgery with malignant transformation may simply reflect the statistical intersection of the frequent use of this therapeutic modality with the highly uncommon development of a malignant vestibular nerve tumor. In the subset of cases in which GKRS was used as a treatment for recurrent tumor, the use of GKRS
may merely show that the tumors had re-
curred and transformed secondary to other
mechanisms. Given the rarity of malignant
vestibular nerve tumors and the more recent
routine use of the MIB-1 labeling index to as-
sess tumor growth potential, the relationship
between GKRS, mitotic index, and malignant
transformation remains unclear. Future case
reports of vestibular schwannomas that have
undergone malignant transformation should
include histopathologic analysis of the mi-
totic index as a means of quantifying the
aforementioned relationships.

The optimal management of malignant
vestibular nerve tumors, regardless of ori-
gin, is uncertain. Several combinations of
aggressive surgical resection and adjuvant
radiotherapy and chemotherapy have been
attempted with poor clinical outcomes. The
median life expectancy after diagnosis of
malignant vestibular schwannomas or
MPNST of the vestibulocochlear nerve is
5–8 months, although some patients have
survived 24 months. Systemic metastasis
has been described (16, 29), generating an-
ecdotal recommendations for craniospinal
MRI and cerebrospinal fluid surveillance
after diagnosis. Conservative radiosurgical
management of recurrent vestibular schwan-
noma has been advocated more recently (51).
Our report suggests that although surgical in-
tervention should be considered for estab-
lished factors, including tumor size
/3 cm, brainstem compression, hydrocephalus, and
neurologic decline, biopsy cannot be recom-
mended merely to determine malignant pro-
gression in the absence of these findings. The
low likelihood of identifying a malignant ves-
tibular nerve tumor and the poor surgical out-
comes for these lesions support repeat radio-
surgery without biopsy.

CONCLUSIONS
Malignant transformation of a benign ves-
tibular schwannoma is an extremely rare
event. As multimodality approaches con-
tinue to be used in the treatment of vestibul-
ar schwannomas, particularly large vestib-
ular schwannomas, cases of malignant
transformation are likely to increase. The
role of radiosurgery in malignant transforma-
tion remains to be elucidated. An ele-
vated MIB-1 labeling index in a benign ves-
tibular schwannoma may increase the risk
of malignant transformation in the setting of
adjuvant GKRS.
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