

Navigating Change and the Acoustic Neuroma Story: Methods, Outcomes, and Myths

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Acoustic neuromas (vestibular schwannomas) are generally slow-growing, intracranial extra-axial benign tumors that usually develop from the vestibular portion of the eighth nerve. Unilateral vestibular schwannomas account for approximately 8% of all intracranial tumors; one of every 100,000 individuals per year develops a vestibular schwannoma.¹⁰³ Bilateral vestibular schwannomas are usually associated with neurofibromatosis 2 (NF2). Both unilateral and bilateral vestibular schwannomas may form as a result of malfunction of a gene on chromosome 22, which produces a protein, Merlin, that controls the growth of Schwann cells. In patients with NF2, the faulty gene on chromosome 22 is inherited and is present in all or most somatic cells. However, in individuals with unilateral vestibular schwannoma, for unknown reasons, this gene loses its ability to function properly and is present only in the schwannoma cells.⁴⁹

A progressive decline in unilateral hearing is the most common symptom that leads to the diagnosis of a vestibular schwannoma.⁴⁴ Only 3 to 5% of patients with vestibular schwannoma have normal hearing at the time of diagnosis. Overall, three separate growth patterns can be distinguished: 1) no or very slow growth; 2) slow growth (i.e., 0.2 cm/yr linear growth on imaging studies); and 3) fast growth (i.e., >1.0 cm/yr). Although most vestibular schwannomas grow slowly, some grow quite quickly and can double in volume within 6 months to 1 year.⁸ A small number of tumors appear to alternate between periods of no or slow growth and rapid growth. Cystic vestibular schwannomas are sometimes capable of relatively rapid enlargement of their cystic component. Spontaneous intratumoral hemorrhage has been rarely described but has occurred mainly in cases of large multicystic tumors.⁹⁹ Using high-resolution scans such as magnetic resonance imaging (MRI), these tumors can be distinguished easily. With the addition of stereotactic radiosurgery, management options have expanded for many patients.

Management Methods and Outcomes

Early diagnosis of a vestibular schwannoma is key to preventing its serious consequences. There are three primary options for managing a vestibular schwannoma: 1) surgical removal; 2) radiosurgery; and 3) observation with serial imaging studies. In addition, some centers suggest conformal fractionated radiation therapy using linear accelerators or proton beam radiation.

Observation with Serial Imaging

In some cases, usually elderly or medically infirm patients or individuals with very small tumors, it may be reasonable to “watch” the tumor for potential growth.³⁵ Repeat MRI scans over time are used to carefully monitor the tumor for any growth.¹⁰⁵ The object of serial observation is to obviate treatment unless signs of growth are confirmed.^{35,76} In our 20-year experience, 70% of tumors under observation have measurable growth in 5 years and almost all by 10 years (Table 6.1).

Surgical Removal

A variety of surgical approaches can be used to remove vestibular schwannomas. The three main routes in general use are the retrosigmoid, translabyrinthine, and middle fossa approaches.^{31,32} Multiple considerations go into deciding which operation is appropriate for an individual patient. These variables include preoperative hearing levels in both ears, tumor size and location, age of the patient, associated medical risk factors, and patient and surgeon preference. Since the outcomes of surgical removal at centers of excellence have improved markedly during the last 2 decades, why should patients consider other management strategies?

Functional Outcome of Microsurgery

Facial Function

Preservation of facial function varies according to tumor size and the surgeon’s experience.⁸⁴ When tumors are smaller than 1.5 cm, good facial nerve function can be expected (House-Brackmann Grades I to II) in more than 90% of patients who have surgery at centers of excellence. Only 3.2 to 6.7% of patients with smaller tumors have poor facial nerve outcomes

TABLE 6.1. University of Pittsburgh Center for Image-guided Neurosurgery acoustic neuroma radiosurgery experience, 1987 to 2007

	No. of Patients	Percent
Total experience	1277	
Primary management	1075	84%
Adjuvant management	202	16%
Primary symptoms		
Hearing loss	1128	88.40%
Balance disorder	603	47.20%
Tinnitus	628	49.20%

(House-Brackmann Grades III to V). In addition to tumor size, intraoperative electrophysiological facial nerve monitoring assists the surgeon in saving the nerve.⁵⁹ The overall facial nerve anatomic preservation rate is 80%.⁶⁶ However, facial nerve function (Grades I and II) can be preserved in only 40 to 50% of patients with large (>4 cm diameter) tumors.¹¹⁰ Injuries of the nervus intermedius are underestimated because this nerve is rarely assessed preoperatively.⁴² A more conservative subtotal resection has been used in the treatment of large symptomatic acoustic neuromas to relieve symptoms of brainstem compression in elderly patients or patients with comorbidities. In these select patients, there is a much higher rate of postoperative facial nerve function (Table 6.2).

Hearing Outcome

The ability to preserve hearing has increased substantially over the recent 2 decades. Depending on the criteria used for reporting successful hearing conservation, hearing preservation has been reported in 30 to 80% of patients considered eligible for hearing preservation surgery.⁸² A meta-analysis performed by Gardner and Robinson in 1988 revealed an overall average success rate of approximately 33%.²⁹ Delayed hearing

TABLE 6.2. Acoustic neuroma radiosurgery outcomes, 1987 to 2007, Center for Image-guided Neurosurgery at the University of Pittsburgh Medical Center

	Early Management (1987–1991)	Current Management (1992–2007)
Imaging	CT	MRI
Marginal dose	16–20 Gy	12.5–13 Gy
Dose planning	Kula	Leksell gamma plan
Tumor control	98%	98%
Hearing preservation	51%	60%–74%
Facial neuropathy	21	<1%
Trigeminal Neuropathy	27	<5%

CT, computed tomography.

deterioration may occur days to years after surgery in 30 to 50% of patients who originally had successful hearing preservation.^{6,9,92,95} In various studies, serviceable hearing preservation rates vary from 8 to 57%^{9,60,85} using the retrosigmoid approach and from 32 to 68%⁸⁵ using the middle fossa approach.

Tinnitus

Tinnitus becomes worse in 6 to 20% of individuals after tumor removal. In the majority of individuals, tinnitus remains unchanged. Approximately 25 to 60% of patients experience a decrease in tinnitus. Of patients without preoperative tinnitus, 30 to 50% developed it in the immediate postoperative period. Tinnitus appears to mimic phantom limb pain in the sense that it may remain even in the absence of preserved hearing.

Complications

Cerebrospinal fluid (CSF) leakage through either the surgical incision or the eustachian tube and middle ear occurs in 2 to 20% of patients.^{2,6,86,90,95} Although in individual published reports, the CSF fluid leak rate appears higher with the retrosigmoid approach (2.9–18%),⁸⁵ a recent meta-analysis suggests similar rates of CSF leak for all surgical approaches (10.6% of 2273 retrosigmoid surgeries; 9.5% of 3118 translabyrinthine surgeries; and 10.6% of 573 middle fossa surgeries). Although CSF leakage sometimes stops spontaneously, reoperation is often necessary to seal the leak and thereby reduce the risk of meningitis. The adjunctive use of endoscopy may assist the surgeon to avoid or to detect a CSF leakage.¹⁰⁴ Other rarer perioperative complications include death (0–3%),^{20,83} intracranial hematomas (1–2%), wound hematoma (3%), cerebellar and brainstem edema, hemiparesis, meningitis (1.2%), wound infections (1.2%), abducens nerve paresis (1–2%), and other lower cranial nerve injuries (Table 6.3).^{83,86}

Recurrence/Residual Tumor

Overall, tumor recurrence rates in the published literature are extremely low and in some studies are between 0 and 1% after a translabyrinthine approach.⁸⁹ However, incomplete resection of vestibular schwannomas is associated with a significant risk of tumor progression requiring subsequent intervention.¹⁹

The Patients' Perspective on Surgical Outcome

A variety of complications have been reported after vestibular schwannoma surgery.^{5,7,17,18,30,37,97} Bateman et al. described patients' subjective condition after vestibular schwannoma surgery as impairment (141 [51%]), disability (95 [34%]), or handicap (43 [15%]).⁴ Most of the impairments were related to problems with facial nerve function. The other most common issues were "balance problems" (19 of 141 [13%]) followed by "hearing loss" (17 of 141 [12%]) and "difficulty with background noise" (14 of 141 [10%]). Tinnitus accounted for five of 141 responses (4%). Disabilities resulting from facial nerve dysfunction accounted for most of the disabilities reported by

TABLE 6.3. Acoustic neuroma outcomes after stereotactic management

Author	Year	Technique	No. of Patients	Tumor		Margin Dose (Gy)	Isodose	No. of Fractions	Follow Up	Percent Tumor Control	Cranial Nerve Preservation		
				Diameter/Volume	Dose						Hearing	Facial	TGN
Weber	2003	Proton	88	1.4 mL	12	70%			38 mo	93.6	33.30%	91%	89%
Harsh	2001	Proton	64	2.5 mL	12	70%			44 mo	94	33%	95.30%	86%
Sawamura	2003	LINAC-SRT	101	19 mm	40–50	90%		5–6 wk	45 mo	91.4	71%	96%	86%
Szumacher	2002	LINAC-SRT	39	20 mm	50	90%		5 wk	21.8 mo	95	67%	95%	95%
Chung	2003	LINAC-SRT	27	2.6 mL	45	90%		5 wk	27 mo	100	57%	100%	100%
Fuss	2000	LINAC-SRT	42	5.5 mL	57.6	90%			42 mo	97.5	85%	100%	95%
Flickinger	2004	GK	313	1.1 mL	13	50%		Single	24 mo	98.6	78.6%	100%	95%
Delbrouck	2003	GK	95			50%		Single	12 mo		67%		
Unger	2002	GK	278	3.8 mL	12	50%		Single	88 mo	93	55%	98.20%	99%
Lunsford	2004	GK	829	2.5 mL	13	50%		Single	10 yr	97	50–70%	99%	97%

TGN, trigeminal neuralgia; GK, gamma knife.

patients. A significant number of disabilities were associated with balance problems (e.g., “unable to drive,” “problems changing direction,” “unable to swim, cycle, run, climb steps, do aerobics,” and “problems bending down”) and with hearing loss (e.g., “difficulty locating the source of sounds,” “difficulty following conversations in a crowd,” “unable to hear people to one side,” and “unable to hear doorbell/telephone”). Some patients reported symptoms of social isolation after the surgery. Fifteen of 43 responses (35%) were “reluctance to attend large social gatherings.” Employment-related problems were also important with seven of 43 responses (16%).

In a retrospective study of 541 Acoustic Neuroma Association members, Wiegand and Fickel stressed that eye-related problems were experienced by 84% of respondents.¹⁰⁷ Each respondent was asked to characterize the most difficult aspect of his or her experience. Thirty percent said that it was the change in appearance, 19% the hearing loss, 16% the loss of independence, and 14% the eye problems. Of interest, 38% of patients experienced depression and 10% had sexual dysfunction.¹⁰⁷ Even by 2007 and despite dramatic advances in the outcome of microsurgery, an alternative management strategy was needed for patients with acoustic neuromas.

Stereotactic Radiosurgery

Vestibular schwannoma stereotactic radiosurgery using the gamma knife was first performed by Leksell in 1969.⁵¹ George Norén, a patient disciple of Leksell, was the first neurosurgical pioneer in the radiosurgical management of acoustic tumors. His initial experience paved the way for introduction and assessment of radiosurgery as an option for patients with these tumors. During the past 2 decades, radiosurgery has emerged as an effective alternative to surgical removal of small- to moderate-sized vestibular schwannomas. The evolution of radiosurgery has changed the management algorithm for treat-

ment (Fig. 6.1). Long-term results have established radiosurgery as an important minimally invasive alternative to microsurgery. Advanced multi-isocenter dose planning software, high-resolution MRI for targeting, and dose optimization over the past 20 years reflect the evolution of this technology. The recent introduction of robotics (automated positioning systems) as part of the gamma knife has further improved dose planning conformity (ability to conform the dose to the target) and selectivity (ability to reduce the dose to surrounding structures). Other image-guided linear accelerator devices generally are useful to fractionate radiation delivery in five to 30 sessions. Proton beam technology is also used to deliver fractionated radiation therapy. The goals of vestibular schwannoma radiosurgery are to prevent further tumor growth, preserve cochlear and other cranial nerve function where possible, to maintain or to improve the patient’s neurological status, and to avoid the risks associated with open surgical resection.

Radiosurgery Technique for Vestibular Schwannomas

Preradiosurgery Evaluation

Patients with vestibular schwannomas are evaluated with high-resolution MRI (computed tomography may be substituted in patients who cannot undergo MRI scans) and audiological tests that include pure tone average (PTA) and speech discrimination score measurements. Hearing is graded using the Gardner-Robertson modification of the Silverstein and Norell classification and/or the American Academy of Otolaryngology–Head and Neck Surgery guidelines,¹⁴ and facial nerve function is assessed according to the House-Brackmann grading system.³⁸ “Serviceable” hearing (Class I and II) is defined as a PTA or speech reception threshold lower than 50 dB and speech discrimination score better than 50%. The Committee on Hearing

Management Algorithm for Acoustic Tumors

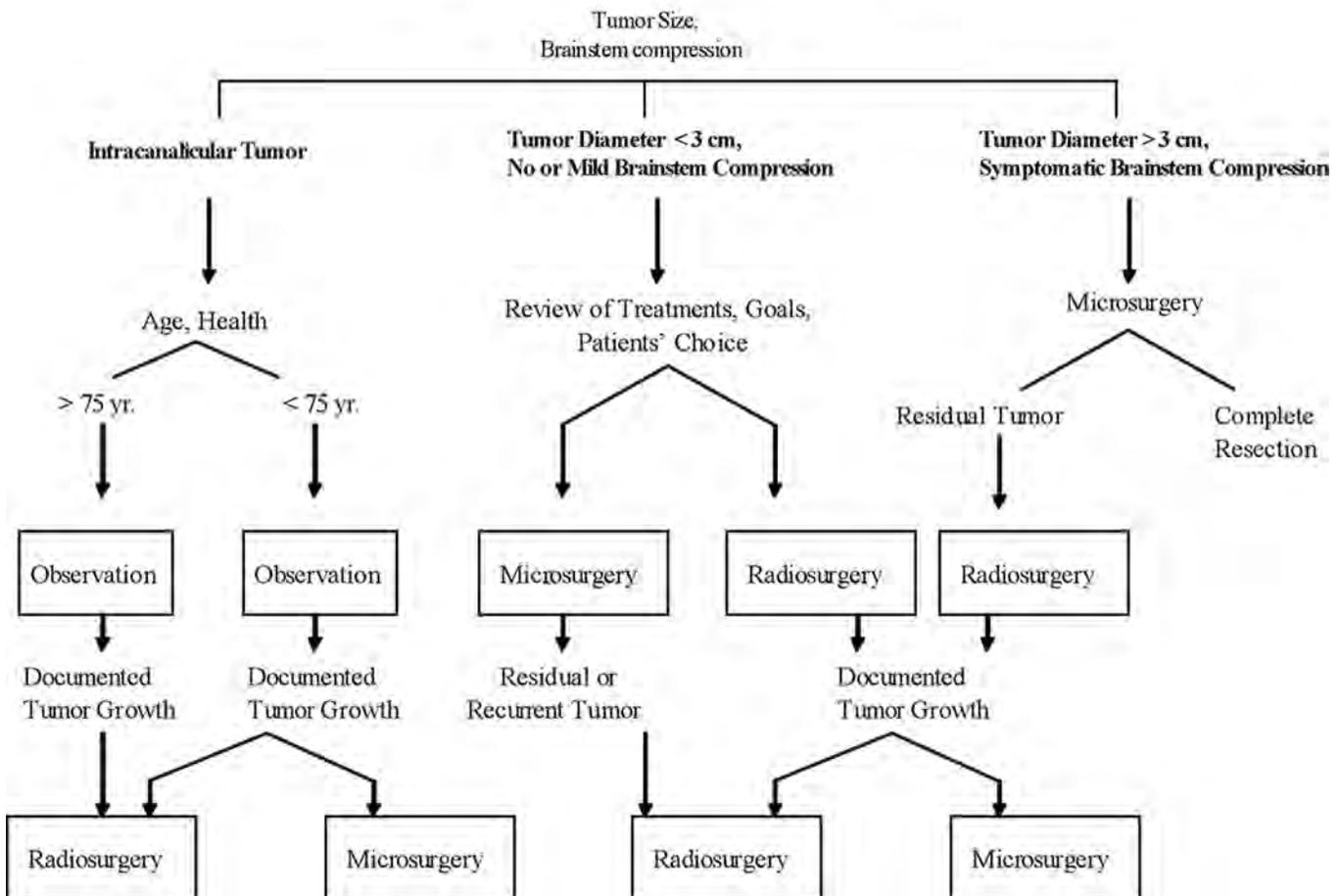


FIGURE 6.1. Suggested algorithm for vestibular schwannoma management. Risks and benefits of observation, resection, and radiosurgery should be reviewed with patients. Patients' goals and wishes should be considered in helping them select an optimal management option.

and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery has established guidelines for reporting vestibular schwannoma results. In this classification, hearing loss at a higher frequency (3000 Hz) is also included in calculating the PTA. “Serviceable” hearing (Class A and B) is similar to Class I and II Gardner-Robertson hearing classes. Every patient is counseled about the options and risks and benefits of microsurgical and radiosurgical management strategies.

Radiosurgery Technique

Radiosurgery can be performed using the gamma knife, modified LINACs, or the proton beam. Techniques of head frame fixation, stereotactic imaging, dose planning, and dose delivery are different for these three modalities. In gamma knife radiosurgery, the procedure begins with rigid fixation of an MRI-compatible Leksell stereotactic frame (model G; Elekta Instruments, Atlanta, GA) to the patient's head. Local anesthetic scalp infiltration (5% Marcaine and 1% Xylocaine)

is used, supplemented by mild intravenous sedation as needed. High-resolution images are acquired with a fiducial system attached to the stereotactic frame. For vestibular schwannoma radiosurgery, a three-dimensional volume acquisition MRI using a gradient pulse sequence (divided into 1- or 1.5-mm thick 28–36 axial slices) is performed to cover the entire lesion and surrounding critical structures. A T2-weighted three-dimensional volume sequence is performed to visualize cranial nerves and delineate inner ear structures (the cochlea and semicircular canals). Stereotactic images are transferred through a fiberoptic Ethernet to the GammaPlan dose planning computer where images are first checked for any distortion or inaccuracy. Planning is performed on narrow slice thickness axial MRI images with coronal and sagittal reconstructions. Centers using LINAC or proton beam systems may use mask immobilization of the patient's head along with image guidance and typically deliver the radiation

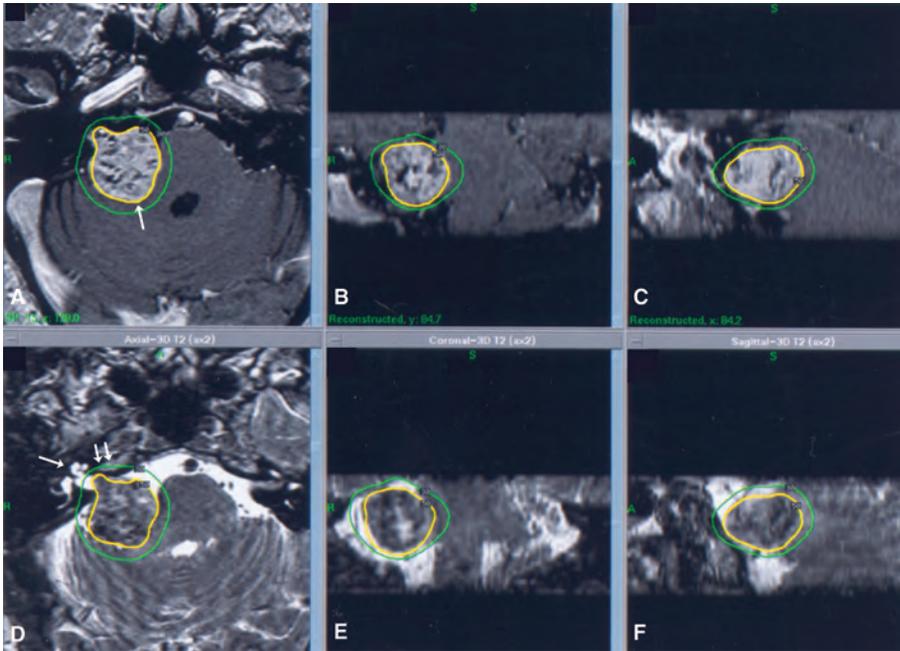


FIGURE 6.2. Conformal gamma knife radiosurgery dose plan for acoustic neuroma. SPGR contrast-enhanced MRI showing conformal dose plan in axial (A), coronal (B), and sagittal (C) planes. A margin dose of 12.5 Gy was prescribed to 50% isodose line (white arrow in A). The isodose lines are projected on three-dimensional T2-weighted images (C–E). The cochlea that is seen in three-dimensional T2-weighted (single arrow in D) images receives less than 5Gy (20%) (double arrow) of the central dose.

dose in five or more fractions over many days. Computed tomography is used for planning at most LINAC sites but may be fused to MRI scans.

Radical Dose Planning

Dose planning is a critical aspect of radiosurgery. Complete coverage of the tumor and preservation of facial, cochlear, and trigeminal nerve function is given priority during dose planning. For large tumors, preservation of brainstem function is also a consideration. A conformal radiosurgery plan is necessary for hearing and facial nerve preservation. Highlights of gamma knife vestibular schwannoma radiosurgery planning include accurate definition of the tumor volume, use of multiple isocenters, beam weighting, and selective use of plug patterns to reduce the dose to critical structures. Precise three-dimensional conformality between treatment and tumor volumes is needed to avoid radiation-related complications.⁵² This degree of conformality can be achieved through complex multi-isocenter planning (Fig. 6.2). Vestibular schwannoma planning is usually performed using a combination of small beam diameter (4- and 8-mm) collimators. For large tumors, 14- to 18-mm collimators are used. A series of 4-mm isocenters are used to create a tapered isodose plan to conform to the intracanalicular portion of the tumor. Success of vestibular schwannoma radiosurgery depends on high conformality to the tumor margin. Because the facial and the cochlear nerve complex generally courses along the anterior margin and anterior–inferior side of the tumor, the dose plan must be highly conformal in this region.

Dose Prescription

After optimizing the plan, a maximum dose inside the target is determined as well as the dose to the tumor edge. The

treatment isodose, maximum dose, and dose to the margin (edge) are jointly decided by a neurosurgeon, radiation oncologist, and medical physicist and, in some centers, a neurotologist. In gamma knife radiosurgery, a dose of 12.5 to 13 Gy is typically prescribed to the 50% (or other) isodose line that conforms to the tumor margin. Dose prescription for vestibular schwannomas changed significantly during the first 10 years' experience at our center. A margin dose of 12 to 13 Gy is associated with a low complication rate and yet maintains a high rate of tumor control as we have found in our most recent 10-year experience using these doses. We suspect that further dose reduction is unwarranted because the tumor control rate will almost certainly worsen and cranial nerve preservation will not improve. Most centers are reluctant to prescribe lower margin doses (such as 12 Gy) for vestibular schwannomas. These same doses of 12 to 13 Gy at the tumor margin are also used for recurrent tumors that undergo adjuvant radiosurgery; such tumors may be more biologically aggressive and, in any case, such patients usually do not have residual serviceable hearing. Similar radiosurgery doses are also used for patients with bilateral (NF2-related) vestibular schwannomas and for patients with contralateral deafness from other causes for whom hearing preservation is highly desirable. After prescribing the margin dose, the falloff on the cochlea, semicircular canals, and brainstem is assessed. Delivery of 12.5 Gy to the edge of the tumors (usually meaning a maximum point in the tumor receives twice that dose) appears radiobiologically equivalent to 50 Gy of fractionated radiation therapy. Of course, the majority of the tumor volume is receiving a radiobiological dose greatly exceeding the equivalent dose delivered by fractionated image-guided radi-

ation therapy. Thus, an edge radiosurgical dose of 12.5 Gy is equivalent to 50 Gy of fractionated radiation therapy given at 1.8 Gy per fraction.²⁵ The maximum radiosurgical dose of 25 Gy is radiobiologically equivalent to 100 Gy of fractionated radiation.²⁴

Dose Delivery

Gamma knife radiosurgery is performed with the 201 source, cobalt-60 unit (Model B or Model C; Elekta Instruments, Stockholm, Sweden) or, more recently, the 192 source Perfexion unit. The patient's head and stereotactic frame are immobilized within the appropriate collimator helmet at a calculated target coordinate. Dose delivery is accomplished in a single session by positioning the head serially for each subsequent isocenter until a fully conformal field encompasses the tumor volume.

Postoperative Care

We give each patient a single intravenous dose of methylprednisolone immediately after radiosurgery. Some centers do not use steroids at all before, during, or after radiosurgery. At other centers, 6 mg of dexamethasone is given immediately before dose delivery and is repeated every 3 hours for the duration of the treatment. The stereotactic frame is removed immediately after radiosurgery. Patients are observed for a few hours in the same-day surgery unit and then discharged.

Postradiosurgery Evaluations

After radiosurgery, all patients are followed up with serial contrast-enhanced gadolinium-enhanced MRI scans, which are generally requested at 6 months, 12 months, and 2, 4, 8, and 16 years. All patients who have detectable hearing before radiosurgery are requested to obtain audiological tests (PTA and speech discrimination score) near the time of their follow-up MRI.

Gamma Knife Radiosurgery: Clinical Results

Tumor Growth Control

Long-term results of gamma knife radiosurgery for vestibular schwannomas have been documented.^{12,22,34,46,48,57} Recent reports suggest a tumor control rate of 93% to 100% after radiosurgery.^{12,16,21–23,26,33,34,36,39,40,45–48,52–54,56,57,64,69,70} Kondziolka et al. studied 5- to 10-year outcomes in 162 patients with vestibular schwannoma who had radiosurgery at the University of Pittsburgh.⁴⁷ In this study, a long-term 98% tumor control rate was reported. The mean dose delivered to the tumor margin in this series of patients was 16.6 Gy (range, 12–20 Gy). The mean maximal dose was 32.7 Gy (range, 24–50 Gy). The specific doses for individual patients were selected according to factors that included tumor volume, surgical history, hearing status, facial motor function, and the patient's wishes. Sixty-two percent of tumors became smaller, 33% remained unchanged, and 6% became slightly larger. Some tumors initially enlarged 1 to 2 mm during the

first 6 to 12 months after radiosurgery as they lost their central contrast enhancement. Such tumors generally regressed in volume compared with their preradiosurgery size. Only 2% of patients required tumor resection after radiosurgery. Norén, in his 28-year experience with vestibular schwannoma radiosurgery, reported a 95% long-term tumor control rate. Litvack et al. reported a 98% tumor control rate at a mean follow-up of 31 months after radiosurgery using a 12-Gy margin dose.⁵⁵ Niranjana et al. analyzed the outcome of intracanalicular tumor radiosurgery performed at the University of Pittsburgh.⁶⁸ All patients (100%) had imaging-documented tumor growth control.

Flickinger et al. performed an outcome analysis of patients with acoustic neuroma treated between August 1992 and August 1997 at the University of Pittsburgh. The actuarial 5-year clinical tumor control rate (no requirement for surgical intervention) was 99.4% ± 0.6% (Fig. 6.3).^{21,22} The long-term (10- to 15-year) outcome of benign tumor radiosurgery has also been evaluated. In a study that included 157 patients with vestibular schwannomas, the median follow-up for the patients still living at the time of the study (n = 136) was 10.2 years. An initial tumor margin dose of 18 to 20 Gy was selected for patients with schwannomas or meningiomas, but by 1989, this dose was reduced to 13 to 18 Gy on the basis of tumor volume, irradiation history, and tumor location in the brain (mean tumor margin doses were vestibular schwannoma, 16.7 Gy; meningioma, 16.5 Gy; other schwannoma, 16.8 Gy; pituitary tumor, 20.8 Gy; craniopharyngioma, 18.5 Gy). Serial imaging studies after radiosurgery (n = 157) showed a decrease in tumor size in 114 patients (73%) (Figs.

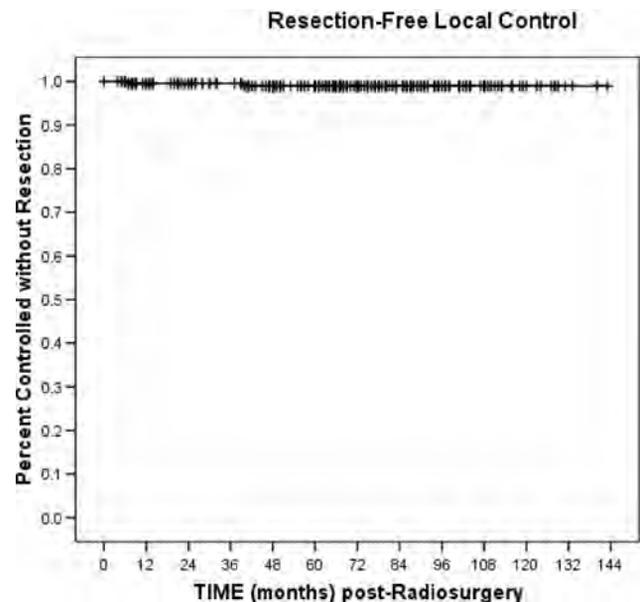


FIGURE 6.3. Kaplan-Meier plot showing 98% tumor control (freedom from need of tumor resection).

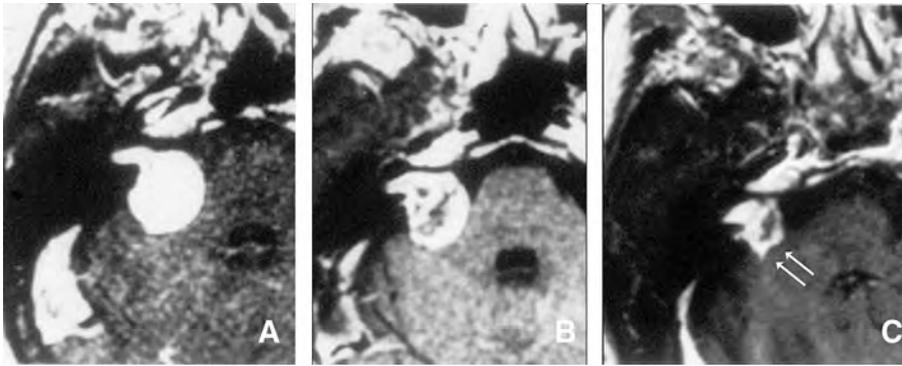


FIGURE 6.4. Axial contrast-enhanced MRI showing right-sided acoustic tumor at radiosurgery (A). Central loss of contrast uptake is noticed at 1-year follow-up MRI (B). A significant tumor shrinkage is seen at 9-year follow-up MRI (C).

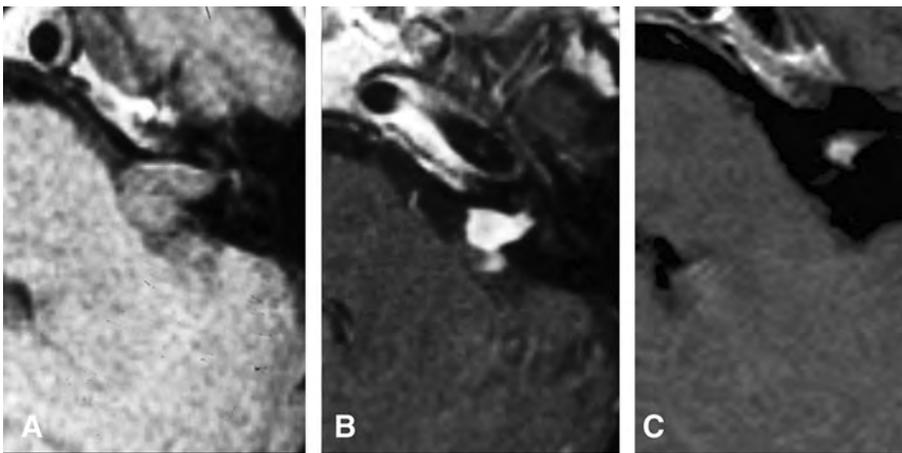


FIGURE 6.5. Axial contrast-enhanced MRI showing a 35-year-old man with a left-sided acoustic tumor at radiosurgery (A). Tumor regression is seen at 2 years (B). Long-term follow-up MRI (C, 19 years) shows significant tumor shrinkage.

6.4 and 6.5), no change in 40 patients (25.5%), and an increase in three patients who later had resection (1.9%).⁴⁸ No patient developed a radiation-associated malignant or benign tumor (defined as a histologically confirmed and distinct neoplasm arising in the initial radiation field after at least 2 yr have passed).

Hearing Preservation

Preradiosurgery hearing can now be preserved in 60 to 70% of patients (Fig. 6.6) with higher preservation rates found for smaller tumors. In a long-term (5- to 10-yr follow-up) study conducted at the University of Pittsburgh, 51% of patients had no change in hearing ability.^{21,47} All patients (100%) who were treated with a margin dose of 14 Gy or less maintained a serviceable level of hearing after intracanalicular tumor radiosurgery.⁶⁸ Among patients treated after 1992, the 5-year actuarial rates of hearing level preservation and speech preservation were 75.2 and 89.2%, respectively, for patients (n = 89) treated with a 13-Gy tumor margin dose (Fig. 6.7A–B). The 5-year actuarial rates of hearing-level preservation and speech preservation were 68.8 and 86.3%, respectively, for patients (n = 103) treated with more than 14 Gy as the tumor margin dose.²²

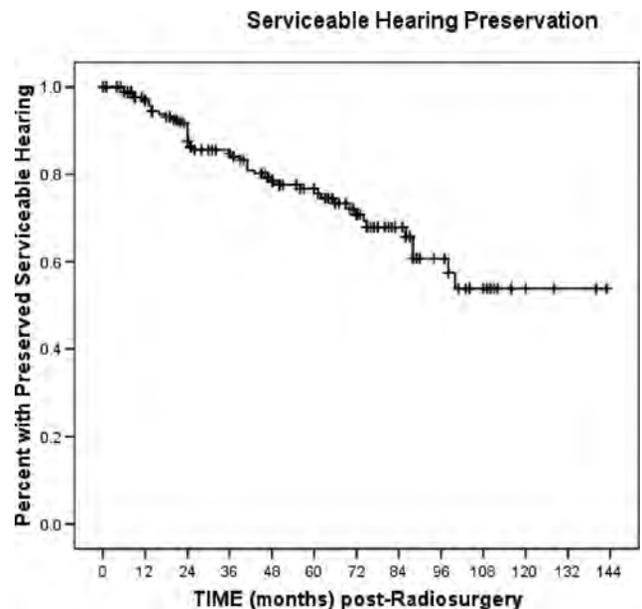


FIGURE 6.6. Kaplan-Meier plot showing 75% serviceable hearing preservation at 5 years.

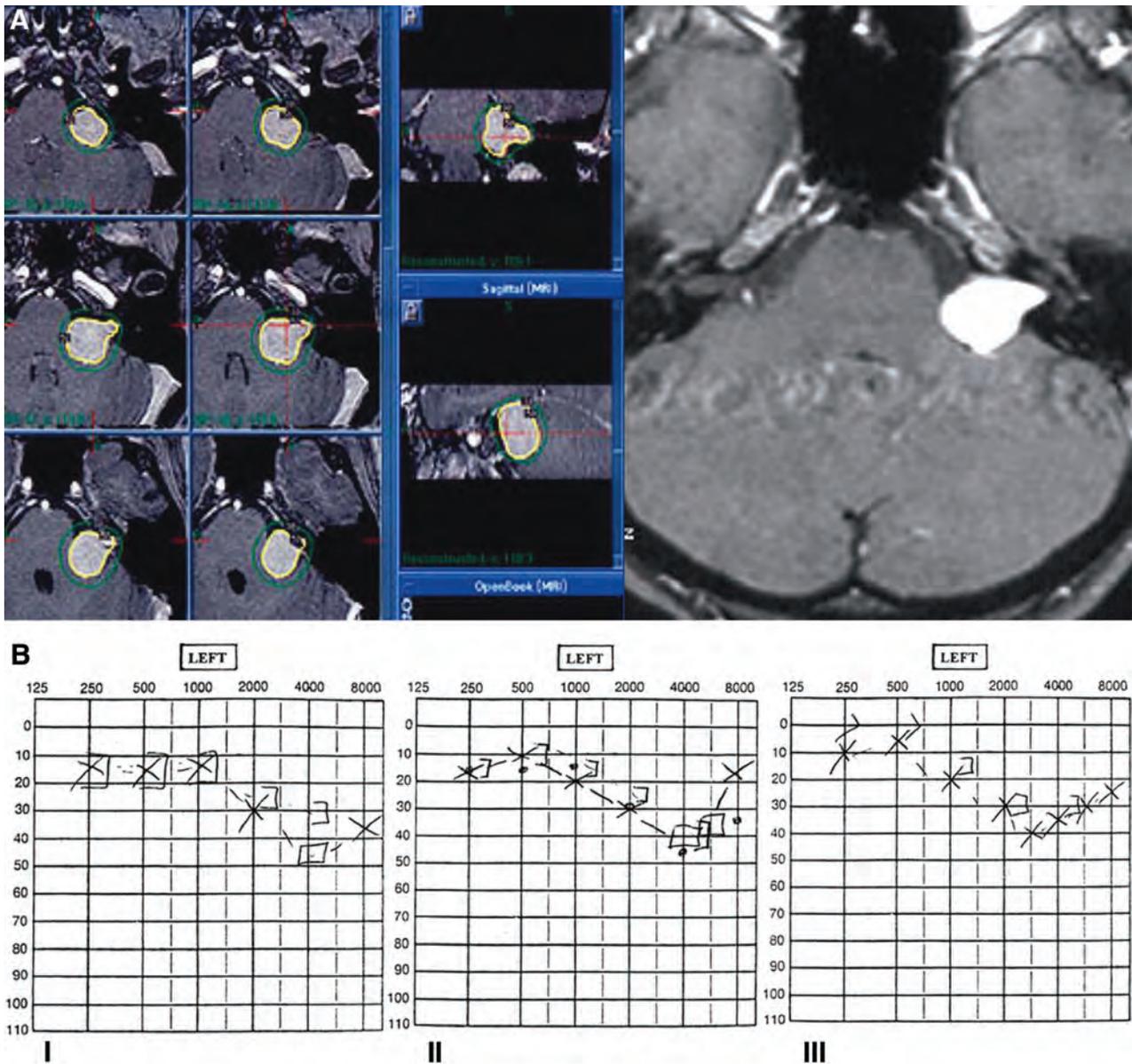


FIGURE 6.7. A, Radiosurgery dose plan for left-sided acoustic tumor with preserved serviceable hearing (left). A follow-up MRI performed at 3 years showing tumor shrinkage (right). B, Audiological tests performed on the same patient at radiosurgery (I, PTA 15 dB, speech discrimination 100%), 1 year (II, PTA 15 dB, speech discrimination 96%), and 3 years (III, PTA 15 dB, speech discrimination 96%) showing preserved serviceable hearing.

Unlike microsurgery, immediate hearing loss is uncommon after radiosurgery. If hearing impairment is noted, it occurs gradually over 6 to 24 months. Early hearing loss after radiosurgery (within 3 mo) is rare and may result from cranial nerve edema or demyelination. The exact mechanism of delayed hearing loss after radiosurgery is still unclear. Perhaps gradual obliteration of microvessels or even direct radiation axonal or cochlear injury is implicated. The effect of radiation on normal microvessels supplying the cochlear nerve or cochlea itself is not known. However, with doses as low as 12

to 13 Gy (which are sufficient to halt the tumor growth), vascular obliteration of normal vessels seems less likely. This dose probably does not adversely affect the vessels as well as the axons. Although with current imaging techniques the cochlear nerve cannot be well visualized, efforts should be made to achieve high conformality at anterior and inferior margins of the tumor. Conformal dose planning using 4-mm collimators for the intracanalicular portion of the tumor may prevent further injury to the cochlear nerve. It is likewise important to avoid radiation of the cochlea.⁷²

Facial Nerve and Trigeminal Nerve Preservation

Facial and trigeminal nerve function can now be preserved in the majority of patients (>95%). In the early experience at the University of Pittsburgh, normal facial function was preserved in 79% of patients after 5 years and normal trigeminal nerve function was preserved in 73%. These facial and trigeminal nerve preservation rates reflected the higher tumor margin dose of 18 to 20 Gy used during the computed tomography-based planning era before 1991. In a recent study using MRI-based dose planning, a 13-Gy tumor margin dose was associated with 0% risk of new facial weakness and 3.1% risk of facial numbness (5-yr actuarial rates). A margin dose of more than 14 Gy was associated with a 2.5% risk of new-onset facial weakness and a 3.9% risk of facial numbness (5-yr actuarial rates).²² Similar 10-year facial and trigeminal neuropathy rates have been documented.¹⁰ None of the patients who had radiosurgery for intracanalicular tumors developed new facial or trigeminal neuropathies.

Neurofibromatosis 2

Patients with vestibular schwannomas associated with NF2 represent a special challenge because of the risk of complete deafness. Unlike the solitary sporadic tumors that tend to displace the cochlear nerve, tumors associated with NF2 tend to form nodular clusters that engulf or even infiltrate the cochlear nerve. Complete resection may not always be possible. Radiosurgery has been performed for patients with NF2. Subach et al. studied our first 40 patients (with 45 tumors) who were treated with radiosurgery for NF2. Serviceable hearing was preserved in six of 14 patients (43%), and this rate improved to 67% after modifications made to the technique in 1992. The actuarial tumor control rate was 98% during the median follow-up period of 36 months.⁹⁸ The mean tumor margin dose was 15 Gy (range, 12–20 Gy).

Only one patient showed imaging documented growth. Normal facial nerve function and trigeminal nerve function was preserved in 81 and 94% of patients, respectively. In the 10 patients for whom more than 5 years of clinical and neuroimaging follow-up results were available (median, 92 mo), five tumors were smaller and five remained unchanged. In two recent series,^{79,80} serviceable hearing was preserved in only 30⁷⁹ and 40%⁸⁰ of cases, respectively. The tumor control rate was, respectively, 71⁷⁹ and 79%.⁸⁰ In the study by Rowe et al.,⁸⁰ the median dose to the tumor margin was 15 Gy with a mean value of 14.6. Mathieu et al. updated outcomes of our NF2 series in 2007.⁵⁸ The tumor control rate was 87.5%. The rate of serviceable hearing preservation using current technique was 52.6%. It now appears that preservation of serviceable hearing in patients with NF2 is an attainable goal using gamma knife radiosurgery. Early radiosurgery when the hearing level is still excellent may become an appropriate strategy in the future. At present, we generally delay radio-

surgery in patients with NF2 until we see hearing deterioration or tumor growth.

Proton Beam Radiosurgery: Clinical Results

Weber et al. evaluated 88 patients with vestibular schwannomas treated with proton beam stereotactic radiosurgery in which two to four convergent fixed beams of 160-MeV protons were applied.¹⁰⁶ A median dose of 12 cobalt Gy equivalents was prescribed to the 70 to 108% isodose lines (median, 70%). The median follow-up period was 38.7 months. The actuarial 2- and 5-year tumor control rates were 95.3 and 93.6%, respectively. Serviceable hearing was preserved in 33.3% of patients. Actuarial 5-year normal facial and trigeminal nerve function preservation rates were 91.1 and 89.4%, respectively. Harsh et al. evaluated 68 patients with vestibular schwannomas who were treated with proton beam using a marginal dose of only 12 Gy.³⁴ After a mean clinical follow-up of 44 months and imaging follow-up of 34 months, actuarial control rates of 94% at 3 years and 84% at 5 years were reported. Cranial neuropathies included persistent facial hypoesthesia (4.7%), intermittent facial paresthesias (9.4%), persistent facial weakness (4.7%) requiring oculoplasty, transient partial facial weakness (9.4%), and synkinesis (9.4%).

LINAC Radiosurgery: Clinical Results

Suh et al. evaluated 29 patients treated with a modified LINAC stereotactic radiosurgery system.¹⁰⁰ The median margin dose was 16 Gy. The 5-year local disease control rate was 94%. Long-term complications included new or progressive trigeminal and facial nerve deficits with estimated 5-year incidences of 15 and 32%, respectively. Subjective hearing reduction or loss occurred in 14 of the 19 patients (74%) who had useful hearing before treatment. Because there was a high risk of cranial nerve neuropathy, these authors did not recommend using only computed tomography-based planning and high prescription doses. Spiegelman et al. reported their results of LINAC radiosurgery for 44 patients with vestibular schwannomas.⁹⁶ After a mean follow-up period of 32 months (range, 12–60 mo), 98% of the tumors were controlled. The actuarial hearing preservation rate was 71%. New transient facial neuropathy developed in 24% of the patients and persisted to a mild degree in 8%.

Stereotactic Radiation Therapy: Clinical Results

Stereotactic radiation therapy (SRT) or fractionated SRT refers to the delivery of a standard fractionation scheme of radiation used with rigidly applied or relocatable stereotactic guiding devices. Some LINAC-based radiosurgery centers (driven by the desire to reduce complication rates) have shifted to fractionated stereotactic radiotherapy for vestibular schwannomas.^{40,63,71,81,88,94,100,102} Ishihara et al. reported 94% tumor control rate at a median follow-up of 31.9 months in a series of 38 patients who had CyberKnife SRT for vestibular schwannoma. One patient developed transient facial paresis (2.6%) and one developed trigeminal nerve neuropathy

(2.6%).⁴⁰ Fuss et al. described 51 patients with vestibular schwannomas who were treated with SRT.²⁷ The mean follow up was 42 months and the actuarial 5-year tumor control rate was 95%. One patient developed a transient facial nerve paresis and two noted new trigeminal dysesthesias. Chung et al., using SRT for 25 patients with useful hearing, reported 57% hearing preservation at 2 years.¹¹ The mean pre- and post-SRT speech recognition threshold was 20 and 38 dB, respectively. The mean proportion of pre- and post-SRT speech discrimination was 91 and 59%, respectively.

Sawamura et al. treated 101 patients with vestibular schwannoma using fractionated SRT to a total dose of 40 to 50 Gy administered in 20 to 25 fractions over a 5- to 6-week period.⁸⁸ The median follow-up period was 45 months, and the actuarial 5-year rate of tumor control was 91.4%. The actuarial 5-year rate of useful hearing preservation (Gardner-Robertson Class I or II) was 71%. The complications of fractionated SRT included transient facial nerve palsy (4%), trigeminal neuropathy (14%), and balance disturbance (17%). Eleven patients (11%) who had progressive communicating hydrocephalus after fractionated SRT required a shunt.

Meijer et al. performed a single-institution trial to study whether fractionated stereotactic radiation therapy is superior to single-session LINAC-based radiosurgery with respect to treatment-related toxicity and local control in patients with vestibular schwannomas.⁶² These authors analyzed 129 patients with vestibular schwannoma who were treated at a LINAC-based radiosurgery facility. Stereotactic radiation therapy was performed on 80 patients with a relocatable guidance device using 5×4 Gy and later 5×5 Gy at the 80% isodose. Forty-nine patients had stereotactic radiosurgery of 1×10 Gy and later 1×12.5 Gy at the 80% isodose using a stereotactic frame. There was no statistically significant difference between the single-fraction group and the fractionated group with respect to mean tumor diameter (2.6 versus 2.5 cm) or mean follow-up time (both 33 mo). Outcome differences between the single-session group and the fractionated treatment group with respect to 5-year local control probability (100 versus 94%), 5-year facial nerve preservation probability (93 versus 97%), and 5-year hearing preservation probability (75 versus 61%) were not statistically significant. The difference in 5-year trigeminal nerve preservation (92 versus 98%) reached statistical significance ($P = 0.048$). These authors concluded that LINAC-based radiosurgery was as good as LINAC-based fractionated stereotactic radiation therapy in patients with vestibular schwannoma, except for a small difference in trigeminal nerve preservation rate in favor of a fractionated schedule.

At the present time, there are limited data on SRT for vestibular schwannomas.¹⁵ There are no compelling radiobiological principles supporting the use of SRT over radiosurgery for achieving an optimal therapeutic response for the slowly proliferating, late-responding tissue of a schwannoma.

Radiosurgery is an effective option but one that requires very high conformality and selectivity of dose delivery as seen using the gamma knife technology. The long-term results (5–10 yr) of SRT are not yet available. For those centers who cannot achieve the necessary conformal plan to permit radiosurgery, SRT may be an option for vestibular schwannomas if they have a higher complication rate using LINAC radiosurgery.

Comparison of Radiosurgery and Microsurgery Options

A recent review of the English language literature published over 23 years (111 articles) found no Level 1 or 2 evidence to support either surgical resection or radiosurgery and highlighted the potential need for prospective trials.⁶⁷ However, it must be recognized that a randomized clinical trial will probably never be completed to compare surgical resection with radiosurgery for vestibular schwannoma. Several carefully performed retrospective studies have compared the results of microsurgery and stereotactic radiosurgery. Karpinos et al. analyzed 96 patients with unilateral acoustic neuromas treated with the Leksell gamma knife or microsurgery and concluded that radiosurgery was associated with a lower rate of immediate and long-term development of facial and trigeminal neuropathy, postoperative complications, and hospital stay. Radiosurgery yielded better measurable hearing preservation than microsurgery and equivalent serviceable hearing preservation rate and tumor growth control.⁴³

Pollock et al. studied 87 patients with unilateral, previously unoperated vestibular schwannomas with an average diameter of less than 3 cm treated at the University of Pittsburgh between 1990 and 1991.⁷⁴ In this matched cohort trial, preoperative patient characteristics and average tumor size were similar between the treatment groups. Microsurgical or radiosurgical techniques were used by experienced surgeons in both treatment groups. The treatment groups were compared based on cranial nerve preservation, tumor control, postoperative complications, patient symptomatology, length of hospital stay, total management charges, effect on employment status, and overall patient satisfaction. Stereotactic radiosurgery was more effective in preserving normal postoperative facial function and hearing preservation with less treatment-associated morbidity. Effect on preoperative symptoms was similar between the treatment groups. Postoperative functional outcomes and patients' satisfaction were greater after radiosurgery when compared with microsurgery. Patients returned to independent functioning sooner after radiosurgery. Hospital length of stay and total management charges were less in the radiosurgical group.

In a similar study of patients with vestibular schwannoma, Régis et al. used objective results and questionnaire answers to compare the results of radiosurgery (97 consecutive patients) with a microsurgery group (110 patients who fulfilled the inclusion criteria).⁷⁷ Questionnaire answers indi-

cated that 100% of patients who underwent gamma knife radiosurgery compared with 63% of patients who underwent microsurgery had no new facial motor disturbance. Ninety-one percent of patients treated with gamma knife radiosurgery, and 61% in the microsurgery study, had no functional deterioration after treatment. The mean hospitalization stay was 3 days after gamma knife radiosurgery and 23 days after microsurgery. All working patients who underwent gamma knife radiosurgery kept the same professional activity compared with 56% in the microsurgery arm. The mean time away from work was 7 days for gamma knife radiosurgery compared with 130 days for the microsurgery group. Among patients whose preoperative hearing level was Class 1 according to the Gardner and Robertson scale, 70% had preserved functional hearing after gamma knife radiosurgery (Class 1 or 2) compared with only 37.5% in the microsurgery group. At 4 years of follow-up, gamma knife radiosurgery provided better functional outcomes than microsurgery. It was concluded that stereotactic radiosurgery was an effective and less costly management strategy for unilateral vestibular schwannomas less than 3 cm in diameter and should be considered a primary management option.

In a recently published study, Myrseth et al. compared the quality-of-life outcomes for 189 patients with acoustic neuroma with tumors less than 30 mm in diameter who were treated with either microsurgery or radiosurgery.⁶⁶ The outcome analysis included assessments of tumor control, cranial nerve preservation rates, and complications. The results showed that cranial nerve function and overall patient outcomes were better in the radiosurgery group. The results reveal that, from the patients' perspective, radiosurgery provides a more desirable outcome than microsurgery.

Radiosurgery After Failed Microsurgery

Pollock et al. analyzed patient outcomes to define the role of radiosurgery in patients who had undergone prior microsurgical resection of their vestibular schwannomas.⁷³ These authors evaluated the pre- and postoperative clinical and neuroimaging characteristics of 76 consecutive patients with 78 vestibular schwannomas who underwent radiosurgery after previous surgical resection. Forty-three patients (55% of tumors) had significant impairment of facial nerve function (House-Brackmann Grades III to VI) after their microsurgical procedure; 50% had trigeminal sensory loss and 96% had poor speech discrimination (<50%). At a median follow-up of 43 months after radiosurgery, tumor growth control after radiosurgery was achieved in 73 tumors (94%).

Roche et al. reported 60 patients who underwent radiosurgery after one or more attempts at surgical resection.⁷⁸ The mean interval between surgical removal and radiosurgery was 71.5 months. Technical difficulties during the procedure were observed in the 12 patients with NF2, primarily as a result of problems in identifying the target. The median follow-up was

51.6 months and the tumor control rate was 93%. No patient developed facial or trigeminal nerve deficits. One case developed lower cranial nerve deficits as a result of a pontine adverse radiation effect. Radiosurgery proved to be a safe and effective alternative to additional microsurgery in patients in whom the initial microsurgical removal failed. We believe that stereotactic radiosurgery should be considered for all patients who have regrowth or progression of previously surgically treated vestibular schwannomas. The decision on when and how to use radiosurgery remains somewhat complex, but the following variables should be considered as part of a clinical decision algorithm: volume (as opposed to size), patient's symptoms including presence or absence of symptomatic mass effect, headache and ataxia, patient's comorbidities, and current neurological function, including facial, hearing, and other cranial nerve function.

Over the past 20 years, evidence-based medicine has established radiosurgery as an effective primary management strategy for vestibular schwannomas, yet various myths still circulate. In the next section, we try to refute these myths.

Myths

The Tumors Will Grow Eventually Despite Radiosurgery

The data presented here should answer the question. In our experience, 98% of patients have long-term tumor growth control at 10 years.

Long-Term Follow-Up is Not Available

With almost 40 years of experience, this statement is no longer supported by facts. Although virtually no long-term microsurgical experience reports tumor recurrence rates at 20 years, that data is now emerging for radiosurgery.

The Dose Needed for Tumor Control is Still Evolving

In fact, the marginal tumor doses needed for tumor control and cranial nerve preservation have been stable for more than 15 years. The marginal dose of 12.5 to 13 Gy has a 98% tumor control rate, a less than 1% risk of facial neuropathy, and a 50.7% hearing preservation rate.

Tumor Resection Would be Very Difficult if Radiosurgery Failed

We can examine this myth in more detail. Microsurgery is rarely needed after vestibular schwannoma radiosurgery (2–5%). In fact, delayed microsurgery should be offered only in the face of sustained growth documented by imaging. Approximately 2 to 5% of patients at 1 to 2 years have mild tumor enlargement before stabilization or shrinkage. Some surgeons tell patients that resection after radiosurgery in these rare patients may be difficult as a result of the effects of radiation. Pollock et al. addressed this issue by reviewing 13 patients who had delayed microsurgery at a median of 27 months after radiosurgery.⁷⁵ Six of the 13 patients had un-

dergone one or more microsurgical procedures before they underwent radiosurgery. Gross total resection was achieved in seven patients and near gross total resection in four patients. The surgery was described by the responsible surgeon as more difficult than that typically performed for schwannoma in eight patients (most of whom had first failed microsurgery before radiosurgery), no different in four patients, and easier in one patient. At the last follow-up evaluation, three patients had normal or near normal facial function, three patients had moderate facial dysfunction, and seven had facial palsies. These authors concluded that there was no clear relationship between the use of radiosurgery and the subsequent ease or difficulty of delayed microsurgery. Because some patients have temporary enlargement of their tumor after radiosurgery, the need for surgical resection after radiosurgery should be reviewed with the neurosurgeon who performed the radiosurgery and should be performed only when sustained tumor growth is confirmed.

The need for tumor decompression usually arises in patients who had radiosurgery for large vestibular schwannomas. A subtotal tumor resection should be considered for such patients if they require surgical resection of their tumor after radiosurgery. Lee et al. performed a retrospective review of four patients who underwent microsurgical resection of vestibular schwannoma after gamma knife radiosurgery or stereotactic radiation therapy. These authors found no significant scarring that could be attributed to the radiation effect.⁵⁰ Szeifert et al. reviewed 22 patients who underwent surgical resection in a series of 1350 patients undergoing gamma knife radiosurgery. These authors studied the histopathological findings and concluded that radiosurgery works by destroying tumor cells directly (with necrosis or inducing apoptosis) as well as by vascular damage. These authors suggested that patients should not undergo craniotomy solely on the basis of radiological progression of the tumor without clinical deterioration.¹⁰¹

Radiosurgery Should Not be Offered Because of the Risk of Radiation-Induced Cancers

This important concern also deserves consideration. After radiosurgery, delayed malignant transformation of a histologically “benign” vestibular schwannoma to a more aggressive neoplasm is potentially possible.^{3,93} Cases of a radiation-related secondary malignant neoplasm have been reported in patients who underwent radiosurgery. At least one was in a patient treated for a vestibular schwannoma.^{1,28,41,61,65,87,91,109} The observed incidence of secondary tumors after radiosurgery is unclear because neither an accurate denominator nor numerator is known. The estimated risk of such oncogenesis over a 5- to 30-year period (fitting the description of radiation-related cancer) is estimated to be less than one in 1000.⁶¹ More likely, the risk is less than one in 20,000. In our radiosurgery experience, no such case has been defined. We have reported a single patient who died with malignant triton schwannoma after prior radio-

surgery.¹³ This risk of oncogenesis can be compared with the surgical mortality at the Centers of Excellence of 0.5% of patients (one in 200) in the first postoperative month after microsurgery.¹⁰⁸

Radiosurgery is Contraindicated for Cystic Tumors

Cystic tumors have a higher risk of intratumoral hemorrhage and enlargement of a tumor-associated cyst. We have seen one such case in 20 years. Large cystic tumors with symptomatic mass effect require surgical removal or drainage. Some cystic tumors may benefit from subtotal surgery with follow-up radiosurgery. In patients with continued cystic progression despite radiosurgery, stereotactic cyst drainage has been used with limited success. Smaller cystic tumors respond well to radiosurgery and generally shrink more completely.

CONCLUSION

Radiosurgery has become a well-documented management option for patients with acoustic neuroma (vestibular schwannomas). As a minimally invasive strategy, we now know the expected success rate and risks. Like microsurgery, not all radiosurgery technologies are the same. The evolution of radiosurgery has led to enhanced outcomes for patients diagnosed with such tumors.

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