LONG-TERM OUTCOMES AFTER RADIOSURGERY FOR ACOUSTIC NEUROMAS

DOUGLAS KONDZIOLKA, M.D., L. DADE LUNSFORD, M.D., MARK R. MCLAUGHLIN, M.D., AND JOHN C. FLICKINGER, M.D.

ABSTRACT

Background Stereotactic radiosurgery is the principal alternative to microsurgical resection for acoustic neuromas (vestibular schwannomas). The goals of radiosurgery are the long-term prevention of tumor growth, maintenance of neurologic function, and prevention of new neurologic deficits. Although acceptable short-term outcomes have been reported, long-term outcomes have not been well documented.

Methods We evaluated 162 consecutive patients who underwent radiosurgery for acoustic neuromas between 1987 and 1992 by means of serial imaging tests, clinical evaluations, and a survey between 5 and 10 years after the procedure. The average dose of radiation to the tumor margin was 16 Gy, and the mean transverse diameter of the tumor was 22 mm (range, 8 to 39). Resection had been performed previously in 42 patients (26 percent); in 13 patients the tumor represented a recurrence of disease after a previous total resection. Facial function was normal in 76 percent of the patients before radiosurgery, and 20 percent had useful hearing.

Results The rate of tumor control (with no resection required) was 98 percent. One hundred tumors (62 percent) became smaller, 53 (33 percent) remained unchanged in size, and 9 (6 percent) became slightly larger. Resection was performed in four patients (2 percent) within four years after radiosurgery. Normal facial function was preserved in 79 percent of the patients after five years (House–Brackmann grade 1), and normal trigeminal function was preserved in 73 percent. Fifty-one percent of the patients had no change in hearing ability. No new neurologic deficits appeared more than 28 months after radiosurgery. An outcomes questionnaire was returned by 115 patients (77 percent of the 149 patients still living). Fifty-four of these patients (47 percent) were employed at the time of radiosurgery, and 37 (69 percent) remained so. Radiosurgery was believed to have been successful by all 30 patients who had undergone surgery previously and by 81 (95 percent) of the 85 who had not. Thirty-six of the 115 patients (31 percent) described at least one complication, which resolved in 56 percent of those cases.

Conclusions Radiosurgery can provide long-term control of acoustic neuromas while preserving neurologic function. (N Engl J Med 1998;339:1426-33.)

LITTLE information exists about long-term outcomes after radiosurgical or microsurgical treatment of acoustic neuromas. Most reports of microsurgical resection have dealt with results immediately after the procedure[1-8]; only a few have systematically used serial imaging studies to determine recurrence rates 5 to 10 years after the intervention. There are no reports on outcomes such as employment status, patient satisfaction, and patient-reported complications in the years after initial treatment of an acoustic neuroma. Early results after stereotactic radiosurgery for acoustic tumors, determined by means of serial imaging studies and clinical examinations, have been reported.[9-17] Because the tumor is not removed by radiosurgery, only long-term follow-up can determine the effectiveness of this technique. To assess outcomes after radiosurgery for acoustic-nerve tumors, we studied all patients who had undergone radiosurgery at a single center between 1987 and 1992. Outcomes between 5 and 10 years after radiosurgery were determined through the use of serial imaging studies, clinical evaluations, and a survey of patients.

METHODS

Characteristics of the Patients

Stereotactic radiosurgery for a unilateral acoustic tumor (vestibular schwannoma) was performed in 162 patients at the University of Pittsburgh between 1987 and 1992 (Table 1). Patients with type 2 neurofibromatosis were excluded from the analysis. The tumor was on the left side in 82 patients and on the right side in 80. Resection had been performed previously in 42 patients (26 percent); 8 of these patients had undergone two resections, 2 patients had undergone three resections, and 1 patient had undergone four resections. Facial function was normal (House–Brackmann grade 1) in 123 patients (76 percent) but was classified as grade 2 in 12 patients, grade 3 in 9, grade 4 in 7, grade 5 in 4, and grade 6 in 7.[19]

The Gardner–Robertson scale was used to classify hearing function (Table 2).[18] Thirty-two patients (20 percent) had useful hearing before radiosurgery: 15 (9 percent) had grade 1 hearing and 17 (10 percent) had grade 2 hearing. Grade 3 hearing was described by 47 patients (29 percent), grade 4 hearing by 7 patients (4 percent), and grade 5 hearing by 76 patients (47 percent).

Radiosurgery Technique

In all patients, stereotactic radiosurgery was performed with a gamma knife (Elekta Instruments, Atlanta). Gamma-knife radiosurgery provided single-session irradiation of the tumor volume defined by imaging. The procedure was performed with use of

From the Departments of Neurological Surgery (D.K., L.D.L., M.R.M., J.C.F.) and Radiation Oncology (D.K., L.D.L., J.C.F.), University of Pittsburgh, Pittsburgh. Address reprint requests to Dr. Kondziolka at the Department of Neurological Surgery, Suite B-400, University of Pittsburgh Medical Center, 200 Lothrop St., Pittsburgh, PA 15213.

TABLE 1. CHARACTERISTICS OF 162 PATIENTS BEFORE RADIOSURGERY FOR AN ACOUSTIC NEUROMA.

CHARACTERISTIC	VALUE
Age — yr	
Mean	60
Range	28–83
Sex — no. (%)	
Female	91 (56)
Male	71 (44)
Previous resection — no. (%)	
Subtotal	29 (18)
Gross total	13 (8)
Previous fractionated-radiation therapy — no. (%)	1 (0.6)
Hearing level — no. (%)*	
Some loss	157 (97)
Some useful hearing	32 (20)
Facial-nerve function — no. (%)	
Normal	123 (76)
Numbness	37 (23)
Balance problems — no. (%)	101 (62)
Tinnitus — no. (%)	61 (38)
Dysphagia — no. (%)	6 (4)

*Hearing was assessed with the Gardner–Robertson scale.[18]

local anesthesia, which was supplemented with intravenous sedation when necessary. From 1987 through 1990, radiosurgery was guided by computed tomographic (CT) imaging. Patients treated in 1991 and 1992 underwent radiosurgery under the guidance of magnetic resonance imaging (MRI); a prospective comparison study confirmed the accuracy of stereotactic targeting based on MRI.[20] Several irradiation isocenters were identified for use in constructing a radiosurgical plan suitable to the intracanalicular and extracanalicular components of the tumor.[21] In 126 patients (78 percent) the 50 percent isodose line was used to irradiate the tumor margin. The image-integrated planning of doses was performed with a computer. For radiosurgery, the patients lay on the gamma-knife couch and were attached to the gamma-knife collimator helmet with a stereotactic frame.

Initially, the dose delivered to the tumor margin, 18 to 20 Gy, was based on experience in a Swedish study.[22] However, the dose to the tumor margin was decreased to an average of 16 to 18 Gy within the first two years and by 1992 was decreased further, to 14 to 16 Gy. Our serial reevaluation of the cranial-nerve response prompted small decreases in the dose in order to improve preservation of cranial-nerve function.[11,12,23] The mean dose delivered to the tumor margin in this series of patients was 16.6 Gy (range, 12 to 20). The mean maximal dose was 32.7 Gy (range, 24 to 50). 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. After radiosurgery, all patients received a single 40-mg dose of intravenous methylprednisolone and were discharged from the hospital the next morning.

Follow-up Evaluations

Serial imaging studies (MRI, or CT when MRI was contraindicated) were requested every six months for the first two years, annually for the next two years, and then once every two years. Patients who lived far from Pittsburgh underwent the imaging studies at sites near their homes and were evaluated by the referring physicians. Patients in the Pittsburgh region returned to our center for evaluation. In patients who were able to hear, serial audiograms were obtained at 6-to-12-month intervals. Each patient underwent a detailed examination that included testing of the cranial nerves and clinical evaluation of central and peripheral nervous system function. Contrast-enhanced imaging studies were used to define the tumor response and to identify hydrocephalus or any changes around the tumor. Before and after radiosurgery, five separate caliper measurements were made of each tumor as it appeared on the images (three extracanalicular measurements and two intracanalicular), as previously described.[24] Tumor enlargement or regression was defined as a change of ±2 mm found by this method.

Survey of the Patients

A survey of all patients was conducted 5 to 10 years after radiosurgery. The survey questionnaire, which was to be returned by mail, included questions about tumor treatment before the radiosurgery procedure, employment status, and changes in the level of activity after radiosurgery. Patients were asked to indicate whether they had had a complication after radiosurgery and, if so, to describe that complication. Patients were also asked three additional questions: Did gamma-knife radiosurgery meet your expectations? As you look back, was radiosurgery a good treatment choice for you? Would you recommend gamma-knife radiosurgery to a friend or family member with an acoustic neuroma?

RESULTS

Tumor Response and Control after Radiosurgery

Most of the irradiated acoustic tumors decreased in size over time (Fig. 1). At the one-year evaluation, the percentages of imaged tumors that were unchanged, smaller, or larger were 73.8, 25.5, and 0.7 percent, respectively. At year 2 the respective figures were 48.4, 46.9, and 4.7 percent, and at year 3 they were 38.1, 58.8, and 3.1 percent. During the first three years, the proportion of patients with enlarged tumors increased. This change represented either true neoplastic growth of the tumor (four patients) or death of the tumor with expansion of the tumor margins as the central portion of the tumor became necrotic. In the five patients with the latter, subsequent imaging studies confirmed reduction of tumor volume. By the third year after radiosurgery, serial imaging studies had identified progressive tumor growth in four patients. These patients underwent resection. Resection of these tumors was described by the operating surgeons as no different from that of a nonirradiated tumor in the cases of three patients, and as more difficult in one case. Facial-nerve function had deteriorated in three patients.

No further increase in tumor volume was identified in any patient from year 4 to year 10 after radiosurgery. By year 4, the proportion of tumors that had regressed was 63.5 percent, and by year 5 it was 76.0 percent. Imaging evaluations were performed serially at 5 to 10 years in 97 patients. An additional 24 patients had imaging studies at year 4, and 17 patients had studies at year 3. Of the 65 patients from whom images were not obtained after five years, 10 died from unrelated causes, 3 were elderly (older than 80 years) at the time of radiosurgery and were eventually lost to follow-up (they were presumed to

TABLE 2. SCALES FOR ASSESSMENT OF FACIAL-NERVE FUNCTION AND HEARING.

FACIAL-NERVE FUNCTION

SCALE	GRADE	DESCRIPTION
House–Brackmann[19]	1	Normal in all areas
	2	Mild dysfunction (slight weakness on close inspection; complete eye closure)
	3	Moderate dysfunction (obvious but not disfiguring difference between two sides; forehead shows slight-to-moderate movement; complete eye closure with effort)
	4	Moderately severe dysfunction (obvious weakness or disfiguring asymmetry; no forehead movement; incomplete eye closure)
	5	Severe dysfunction (barely perceptible motion)
	6	Total paralysis

HEARING FUNCTION

SCALE	GRADE	DESCRIPTION	PURE-TONE AVERAGE	SPEECH-DISCRIMINATION SCORE
			decibels	percent
Gardner–Robertson[18]	1	Good to excellent	0–30	70–100
	2	Serviceable	31–50	50–69
	3	Nonserviceable	51–90	5–49
	4	Poor	91–100 (maximum)	1–4
	5	None	Not testable	0

have died), 6 refused further imaging but were well and had no new symptoms, 20 could not be located by us or by their referring physicians after the initial imaging reviews, and 26 provided clinical follow-up information but to date have not been available for longer-term imaging. Of the group with at least five years of follow-up, imaging studies showed that 70 patients (72 percent) had a decrease in tumor volume after radiosurgery and 27 (28 percent) had no change in the size of their tumors (Fig. 2).

Clinical Response after Radiosurgery

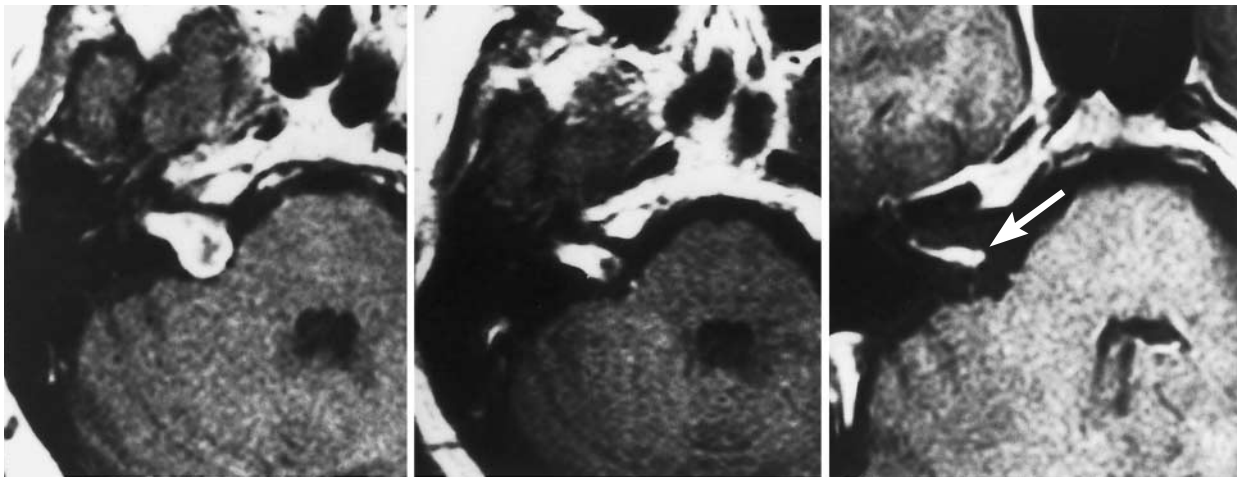
All patients were discharged within 24 hours after radiosurgery. Several patients had headaches that lasted several hours after removal of the stereotactic frame. There were no infections or systemic complications. Patients were allowed to resume their activities and daily routines immediately after discharge. One patient completed a marathon race two days after radiosurgery.

Neurologic evaluations showed that any new or worsened deficits occurred within 28 months after radiosurgery. In addition, no patient described a new neurologic problem between year 3 and year 10 after the procedure. Normal facial-nerve function was preserved in 122 of 155 patients (79 percent) who could be evaluated and in 122 of 144 patients (85 percent) who had normal facial function before radiosurgery. In no patient with normal facial function (House–Brackmann grade 1) who had radiosurgery did complete facial weakness (grade 6) develop. Complete facial weakness was observed only in patients who had a preexisting deficit (grade 3, 4, or 5), usually after a previous resection. The actuarial rate of recovery from a facial-nerve deficit at eight years was 63 percent. Multivariate analysis showed that several factors were related to the onset of facial neuropathy.[25] These included a higher dose of radiation to the tumor margin ($P<0.003$) and a tumor that was larger in transverse diameter than the other tumors ($P<0.003$).

Normal functioning of the trigeminal nerve was

Figure 1. Serial Axial Contrast-Enhanced Magnetic Resonance Images Obtained before and after Gamma-Knife Radiosurgery for Acoustic Neuromas.

Panel A shows images from a 62-year-old man at the time of radiosurgery (left-hand image); after three years (middle image); and after nine years, when only minimal residual tumor is visible (arrow, right-hand image). Panel B shows images from a 73-year-old man at the time of radiosurgery (left-hand image); after one year, when the uptake of contrast is decreased (middle image); and after nine years, when the tumor has regressed and no longer compresses the surface of the brain stem (arrow, right-hand image). Panel C shows images from a 48-year-old man at the time of radiosurgery (left-hand image) and 10 years later, when regression of the extracanalicular component of the tumor is evident (arrow, right-hand image).



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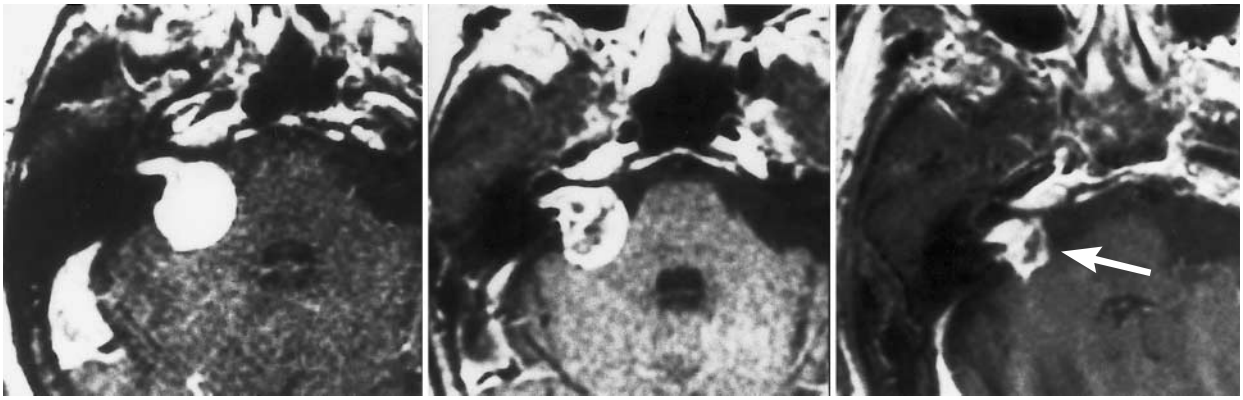

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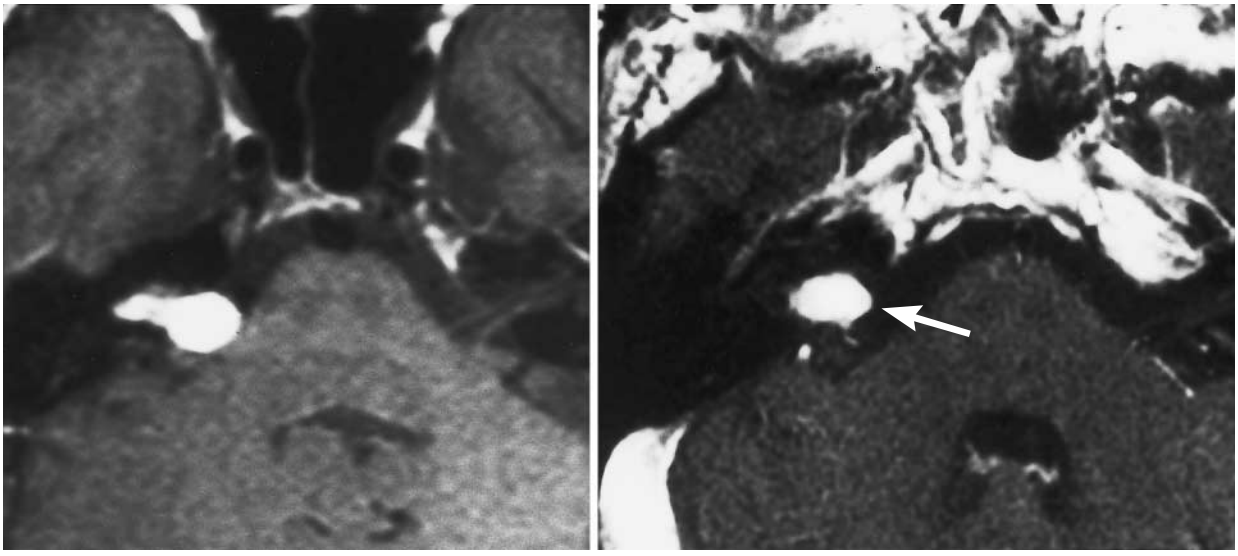

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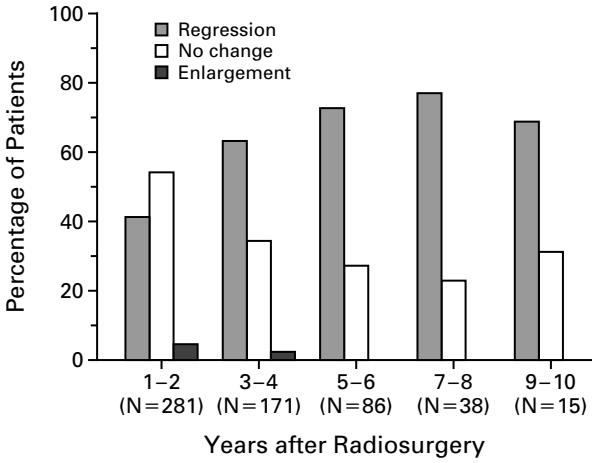

Figure 2. Percentages of Patients in Whom Tumors Regressed, Were Unchanged, or Became Larger during the 10 Years of Evaluation after Radiosurgery.

preserved in 119 of 162 patients who could be evaluated (73 percent) and in 119 of 142 patients who had normal function before radiosurgery (84 percent). In none of the patients with intracanalicular tumors did facial sensory dysfunction develop after radiosurgery. In multivariate testing, the tumor volume and the dose of radiation to the margin were identified as significantly associated with the risk of neuropathy ($P<0.001$).

No change in the Gardner–Robertson hearing grade was found in 43 of 85 patients (51 percent). Of the 32 patients who had useful hearing before radiosurgery (Gardner–Robertson grades 1 and 2), 15 (47 percent) maintained hearing within those levels. Some degree of hearing and sound recognition was preserved in 52 of 85 patients (61 percent). Planning radiation doses on the basis of CT scans, as compared with MRI, was a significant risk factor for hearing loss ($P<0.006$).

No patient had vagal or glossopharyngeal dysfunction; seven patients (4 percent) described new or worsened ataxia; and in three patients, signs and symptoms of hydrocephalus developed and required placement of a ventriculoperitoneal shunt.

Survey of Patients after Radiosurgery

Our survey was returned by 115 patients (77 percent of 149 survivors). Surgery had been performed previously in 30 of them (26 percent). Fifty-four patients (47 percent) were employed at the time of radiosurgery, and 37 of these 54 (69 percent) remained so afterward. Most of the patients who did not remain employed reached retirement age during the course of follow-up. Patients described their overall level of activity as unchanged (68 percent of patients), increased (8 percent), or decreased (24 percent). When asked whether gamma-knife radiosurgery had met their initial expectations, 106 of the respondents (92 percent) said yes. This included 97 percent of respondents who had undergone surgical resection previously and 91 percent of those who had not. Complications were described by 36 patients (31 percent) and resolved in 20 of them (56 percent) (Table 3). Radiosurgery was described as successful by all 30 of the patients who had undergone surgery previously and by 81 (95 percent) of those who had not undergone resection previously. When asked whether they would recommend the procedure to a friend or family member, 109 (95 percent) of the respondents said yes, 2 said no, and 4 said they did not know.

TABLE 3. COMPLICATIONS DESCRIBED BY 115 PATIENTS AFTER RADIOSURGERY FOR AN ACOUSTIC NEUROMA.*

COMPLICATION	NO. OF PATIENTS (%)
Balance problems	7 (6)
Facial twitching	6 (5)
Facial weakness	4 (3)
Tinnitus	3 (3)
Hydrocephalus	3 (3)
Numbness	2 (2)
Headache	2 (2)
Facial pain	1 (1)
Watery eyes	1 (1)
Low blood pressure	1 (1)
Bleeding from tumor	1 (1)
Dizziness	1 (1)
Dry eyes	1 (1)
Unspecified	1 (1)

*Of 149 surviving patients, 115 returned the questionnaire designed to assess patients' satisfaction and level of functioning after radiosurgery.

DISCUSSION

Wiegand and Fickel surveyed 832 patients who were members of the Acoustic Neuroma Association and had undergone a tumor resection between 1973 and 1983 and received responses from 65 percent.[26] Of these 541 patients, there was facial weakness in 62 percent, eye-related problems in 84 percent, depression in 38 percent, sleep disturbance in 26 percent, and speech or swallowing difficulties in 16 percent. Seventy percent of the patients returned to work within four months after the procedure. A more recent survey, of 1579 resections performed between 1989 and 1994, found a 44 percent rate of facial weakness, an 11 percent rate of cerebrospinal fluid leakage (which resolved in most cases without further surgery), and a 9 percent rate of persistent balance problems after one year. Recurrent or per-

sistent tumor was found in 7.8 percent of the patients on follow-up imaging studies.[27]

In contrast, Gormley et al. and Samii and Matthies found that complete tumor removal was a frequent outcome, but in both series the mortality rates were 1 percent and the rates of cerebrospinal fluid fistulas were 9.2 percent and 15 percent, respectively.[2,7] Nevertheless, significant reductions in the rates of post-resection complications have been described over the past 20 years by experienced surgical teams. Slattery et al. found preservation of facial function (House–Brackmann grade 1 or 2) in 95 percent of 151 patients after resections of the middle fossa for tumors a mean of 1.2 cm in diameter.[28] In a series of 39 patients with intracanalicular tumors, Shelton and Hitselberger found that 67 percent of patients retained a measurable degree of hearing and that 97 percent had normal or near-normal facial function one year after the resection.[29] For patients with large acoustic tumors (extracanalicular diameter, >3 cm) and those with progressive neurologic deficits that require decompression of the brain stem, surgical resection is the preferred option. Whether resection under those circumstances should be total or subtotal remains controversial. We believe that resection should be complete in these patients when feasible, but not at the expense of neurologic function. For patients with acoustic tumors that are intracanalicular or small or medium in size, a therapeutic alternative is radiosurgery. Most patients with smaller tumors do not have a rapidly progressive neurologic syndrome yet have persistent hearing loss, balance problems, tinnitus, vertigo, headache, or a combination of these symptoms. These symptoms are not improved consistently by resection or by radiosurgery.[17] Because improvement in symptoms is rare after resection of an acoustic tumor, many patients now prefer to choose a treatment with minimal risk. For many patients this choice is stereotactic radiosurgery.

Before our present understanding of the long-term effects of radiosurgery was achieved, some physicians and patients questioned whether radiosurgery could prevent tumor growth in the long term. There was also little information regarding the rate of recurrence after microsurgical, "gross total" tumor resection. Cerullo et al. reported a 10 percent rate of recurrence within 10 years after resection.[1] Mazzoni et al. studied 104 patients in whom preservation of hearing had been attempted.[4] The overall rate of tumor recurrence was 8.1 percent, including 5 of 46 patients (11 percent) followed for 3 to 17 years. In other attempts to preserve hearing, Post et al. found that in 4 of 56 patients (7 percent) resection was incomplete and that in 3, regrowth occurred within three years.[5] In the largest series, Samii and Matthies were able to achieve complete resection in 98 percent of patients and found late recurrence in 6 (0.7 percent) of 880 who did not have type 2 neurofibromatosis.[7] In our series of patients treated with radiosurgery, 98 percent of patients required no further surgery, and in 94 percent tumor control was confirmed by imaging techniques. Five patients (3 percent) had transient tumor enlargement followed by regression. After three years of follow-up after radiosurgery, no patient had enlargement of the tumor, and most had further regressions in tumor volume. Although we cannot state that with radiosurgery the rate of disease control is better than or similar to the cure rate with surgical resection (because after radiosurgery the tumor mass remains in the patient), the two treatments seem to provide similar rates of prevention of problems due to further tumor growth. For these reasons, we believe that for patients with smaller tumors, radiosurgery provides tumor control as effective as that achieved with microsurgical resection.

Patients with newly diagnosed, residual, or recurrent acoustic tumors less than 3 cm in extracanalicular diameter are suitable candidates for stereotactic radiosurgery. We rarely perform radiosurgery in patients with larger tumors, because the reduction in the dose of radiation necessary to minimize adverse effects on tissue decreases the efficacy of the procedure. In 1987, our inclusion criteria produced a study population consisting of patients with older age, concomitant medical problems that argued against resection, residual or recurrent tumors after resection, and preserved hearing function. Until 1990 we recommended surgical resection to most younger patients, but some refused and underwent radiosurgery. Our early analysis of results from the younger patients showed findings similar to those obtained in older patients. In 1991 we therefore began to offer radiosurgery to all patients with acoustic tumors regardless of age, surgical history, or symptoms. The outcomes in this series did not differ between younger and older patients. We prefer continued observation in older patients (>70 years old) with small and minimally symptomatic tumors[30] who undergo annual imaging studies and receive treatment only when tumor growth or progressive symptoms are documented.

Analysis of our results prompted several refinements in our technique. First, we considered the approximately 30 percent rate of damage to the facial nerves unacceptable, even though damage was delayed and usually mild. The initial rate of trigeminal-nerve dysfunction seemed higher than that after resection, although most resection series did not report this outcome. This finding prompted, in 1989, an average reduction of 2 Gy in the dose of radiation delivered to the tumor margin. Since the rate of complications did not decline, however, we analyzed our method of dose planning. We believed that planning doses according to CT findings was an unsatisfactory approach, since the intracanalicular portion of the tumor could not be well visualized. However, with

MRI, we had a tool that showed the tumor and regional structures, including cranial-nerve anatomy in great detail. For the first time we could perform radiosurgery with meticulous targeting, using multiple small isocenters of irradiation. Advances in high-speed computer workstations facilitated planning. With these refinements, cranial-nerve morbidity decreased considerably, with a rate of facial-nerve and trigeminal-nerve side effects that was below 7 percent for extracanalicular tumors and below 2 percent for intracanalicular tumors. In our study, 49 patients received radiation to the tumor margin at doses of up to 15 Gy and had long-term follow-up, and in this group, the high rate of control of tumor growth was maintained.[31] This finding indicated that the radiation doses initially thought to be necessary for a tumor response were too high. Radiobiologic studies showed that the lower dose range causes tumor regression in human xenograft models.[32]

Although results of more than 10 years of follow-up will be necessary to substantiate the curative effects of radiosurgery, we believe that the present analysis makes several points clear. First, radiosurgery for acoustic-nerve tumors is a well-tolerated surgical procedure and meets most patients' expectations. Second, the proportion of patients with reduction of tumor volume is considerable and is higher than previously believed. Early reports noted a 30 to 40 percent rate of tumor regression,[10] whereas 72 percent of patients in this study with images obtained five or more years after radiosurgery had smaller tumors. Third, when tumor regrowth occurs, it does so early after radiosurgery. Fourth, cranial neuropathy or other neurologic symptoms associated with radiosurgery occur within the first three years after the procedure, are usually transient, and are relatively mild. Fifth, older patients with larger tumors (2 to 3 cm) continue to have a small risk of hydrocephalus (3 percent). This risk is similar to that observed with conservative management or after surgical resection.[2,7] Finally, over the long term, the majority of patients describe radiosurgery as a successful treatment for their acoustic tumors and would recommend it to friends or family. Understanding the foundations of patients' decision making is important as we select methods to analyze results and make recommendations for therapy.[33]

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