

Fractionated Stereotactic Radiosurgery and Preservation of Hearing in Patients with Vestibular Schwannoma: A Preliminary Report

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OBJECTIVE: Microsurgery and stereotactic radiosurgery (SRS) for vestibular schwannomas are associated with a relatively high incidence of sensorineural hearing loss. A prospective trial of fractionated SRS was undertaken in an attempt to preserve hearing and minimize incidental cranial nerve injury.

METHODS: Thirty-three patients with vestibular schwannomas were treated with 2100 cGy in three fractions during a 24-hour period using conventional frame-based linear accelerator radiosurgery. The median tumor diameter was 20 mm (range, 7–42 mm). Baseline and follow-up evaluations included audiometry and contrast-enhanced magnetic resonance imaging. End points were tumor progression, preservation of serviceable hearing, and treatment-related complications.

RESULTS: Thirty-one patients (32 tumors) were assessable for tumor progression and treatment-related complications and 21 patients for preservation of serviceable hearing, with a median follow-up interval of 2 years (range, 0.5–4.0 yr). Tumor regression or stabilization was documented in 30 patients (97%) and tumor progression in 1 (3%). The patient with tumor progression remains asymptomatic and has not required surgical intervention. Five patients (16%) developed trigeminal nerve injury at a median of 6 months (range, 4–12 mo) after SRS; two of these patients had preexisting trigeminal neuropathy. One patient (3%) developed facial nerve injury (House-Brackmann Class 3) 7 months after SRS. Preservation of useful hearing (Gardner-Robertson Class 1–2) was 77% at 2 years. All patients with pretreatment Gardner-Robertson Class 1 to 2 hearing maintained serviceable (Class 1–3) hearing as of their last follow-up examination.

CONCLUSION: Three-fraction SRS with a conventional stereotactic frame is feasible and well tolerated in the treatment of acoustic neuroma. This study demonstrates a high rate of hearing preservation and few treatment-related complications among a relatively high-risk patient cohort (tumors >15 mm or neurofibromatosis Type 2). Longer follow-up will be required to assess the durability of tumor control. (Neurosurgery 45:1299–1307, 1999)

Key words: Acoustic neuroma, Fractionation, Hearing preservation, Radiosurgery, Vestibular schwannoma

Refinement of microsurgical techniques has substantially reduced the morbidity associated with surgical removal of vestibular schwannomas (VSs). The incidence of significant facial nerve injury has declined to less than 10% in several modern series. Preservation of cochlear nerve function continues to pose a significant challenge, however. In a 1988 review of attempted hearing preservation using middle fossa or posterior fossa approaches, only 33% of patients across several surgical series maintained clinically useful

hearing (12). Although there have been improvements in the past decade (38, 40), the overall rate of successful preservation of cochlear function remains 50% or lower and is particularly challenging in patients with moderate- to large-size tumors (>10–15 mm). The inherent difficulty in separating the schwannoma capsule from the vestibulocochlear nerve without causing injury by vascular compromise or neuronal disruption remains a significant obstacle to preservation of hearing with modern microsurgery.

Stereotactic radiosurgery (SRS) is a noninvasive alternative to conventional surgery that is applicable to small and moderate-size (≤ 3 cm) VSs. Pioneered by Leksell, this technique was first used in the treatment of VS in 1969. Since its introduction, SRS has been used in more than 5000 patients with VS worldwide (27), with reported follow-up periods as long as 15 years (36). Although tumor control (90–95% at 5–10 yr) (24) and trigeminal and facial nerve injury rates (10–20%) have been uniformly favorable (8, 31, 36, 37), SRS, like microsurgery, continues to be associated with significant hearing loss. Most studies report preservation of useful hearing in less than 50% of treated patients (10, 18, 23, 24).

Efforts to improve the efficacy and safety of SRS have focused primarily on increasing the precision of tumor localization and conformality of dose deposition to target tissues. Although SRS advances have been associated with reductions in treatment-related morbidity (8), it remains improbable that technical advances can achieve complete exclusion of the cochlear nerve from the high-dose target volume. Because cochlear nerve injury remains a significant limitation of SRS, methods to exploit biological differences among the tumor and surrounding normal cranial nerves should be explored.

For decades, it has been axiomatic that fractionation of therapeutic radiation (delivery of the total therapeutic dose in several smaller fractions during a period of time) enhances tumor susceptibility and allows for the recovery of normal tissues, thereby increasing tumor control and minimizing normal tissue effects. Until recently, rigid fixation of the stereotactic localizing frame has largely precluded the consideration of fractionation in the stereotactic treatment of brain tumors. Recognition of the potential biological advantages of fractionated SRS prompted the development of removable or relocatable stereotactic systems for fractionated SRS programs (13). However, changing from a rigid fixation system to a relocatable frame results in some loss of precision. Furthermore, prolonged standard fractionation lacks the practicality of a single outpatient procedure. In an effort to improve hearing preservation for patients with VS, we designed a fractionated SRS protocol to incorporate the physical advantages of rigid stereotactic localization, the practicality of a 1-day treatment, and the potential biological advantages of an abbreviated fractionation schedule. Our goal has been to maintain a high rate of VS control while reducing incidental damage to the cochlear nerve and preserving serviceable hearing. This article summarizes our results 4 years after the initiation of this program.

PATIENTS AND METHODS

Eligibility and patient characteristics

Between August 1994 and January 1998, 34 VSs in 33 patients were treated with fractionated stereotactic radiosurgery. Eligibility for this treatment protocol required radiographic evidence of a VS with documentation of tumor progression or hearing deterioration within the previous 12 months. Initially, all patients were required to have serviceable hearing in the treated ear by objective (Class 1–3 on the

Gardner-Robertson [GR] scale) (12) or subjective criteria. The eligibility was later expanded to include patients with significant hearing deficits at baseline if there was preexisting trigeminal or facial nerve dysfunction. These patients were included on the basis of the observation that fractionated treatment may also reduce injury to the trigeminal and facial nerves (43).

The study group consisted of 21 men and 12 women. The median age was 50 years (range, 22–88 yr). Ten patients were diagnosed with neurofibromatosis Type 2 (NF2); eight of these patients were deaf in the contralateral ear as a consequence of prior surgical resection ($n = 6$), SRS ($n = 1$), or tumor progression ($n = 1$). Pretreatment audiograms were available for 31 treated ears: 23 were scored as GR Class 1 to 3; 3 patients had Class 4 (detectable) hearing; and 5 patients had Class 5 (not detectable) hearing. Twenty-seven tumors were previously untreated, and seven tumors were recurrent and progressive after previous surgical resection.

Tumor dimensions were determined before treatment and at follow-up on gadolinium-enhanced T1-weighted thin-slice (2–5 mm) magnetic resonance imaging (MRI) of the internal auditory canals. The enhancing lesion was measured along its maximal intracanalicular-cerebellopontine angle length. The other dimensions were obtained along the corresponding perpendicular in the axial plane and the maximal height in the coronal plane. The median maximal tumor diameter in this series was 20 mm (range, 7–42 mm). Four tumors were classified as small (≤ 15 mm), 27 were moderate in size (16–30 mm), and three were large (> 30 mm).

Radiosurgical technique

Patient immobilization and tumor localization were accomplished with rigid cranial fixation using a Brown-Roberts-Wells stereotactic frame (Radionics, Burlington, MA). Imaging for localization and treatment planning was carried out with 1-mm contrast-enhanced computed tomography or MRI through the internal auditory canals and cerebellopontine angle. Treatment planning software was developed at Stanford University. One to four isocenters were used to provide a conformal dose distribution at the periphery of the contrast-enhancing lesion. The typical treatment plan consisted of two isocenters, the larger centered on the cerebellopontine angle component and the smaller on the intracanalicular component. The standard treatment arc arrangement has been described previously (1); it consisted of four noncoplanar arcs per isocenter with individual arc modifications to improve tumor/dose conformality and reduce incidental irradiation of adjacent critical structures. The planned total dose was 2100 cGy via 4-MV or 6-MV linear accelerator photons prescribed to the periphery of the contrast-enhancing lesion. The dose was administered in three equal fractions of 700 cGy during a 24-hour period. Frame placement, imaging, and treatment planning were performed in the afternoon on Day 0, with the first fraction administered early that evening. With the Brown-Roberts-Wells frame in place, the patient was admitted to the ambulatory treatment unit for an overnight stay. Most patients required mild analgesics and sedation for sleep.

The second fraction was administered early the next morning and the third and final fraction in the late afternoon, approximately 24 hours after the first fraction. Immediately after the third treatment, the stereotactic frame was removed and patients were discharged home. Resumption of normal activity was permitted on Day 2.

Patient follow-up

Clinical assessment for neurological injury was performed at 6-month intervals for the first 2 years and annually thereafter. Audiometric and radiographic follow-up was obtained at 6 months, 1 year, and annually thereafter. Trigeminal nerve injury was scored for any paresthesia or anesthesia within the trigeminal distribution. Facial nerve injury was scored according to House-Brackmann criteria (19). Standard audiometric assessments were used to measure pure tone average (PTA), speech reception threshold, and speech discrimination for classification according to the system described by Gardner and Robertson (12). Tumor measurements from thin-section MRI were performed pre- and posttreatment by a single examiner (JCP). Tumor progression was defined as at least a 3-mm increase in any one of the three tumor dimensions. Tumor regression was defined as at least a 3-mm decrease in any one dimension, with either stabilization or decrease in the other dimensions. Tumor stabilization was defined as change less than 3 mm in all three dimensions when compared with pretreatment tumor measurements.

Statistical methods

Univariate analysis was applied to examine the effects of patient age, presence of NF2, presence of preexisting neuropathy, prior conventional surgery, tumor size, computed tomography versus MRI treatment planning, number of treatment isocenters, and dose heterogeneity (as measured by the ratio of the prescribed dose to the maximal dose) on treatment-related complications and preservation of hearing. Actuarial curves were constructed using the methods of Kaplan and Meier (22). Actuarial rates were compared using the log-rank test. Statistical significance was defined as $P \leq 0.05$.

RESULTS

Protocol compliance and follow-up

The treatment protocol was modified twice during the initial phase so that two of the first three patients received doses of 2550 cGy and 1950 cGy. All other patients received 2100 cGy. Thirty-one of 33 patients received three fractions, with a minimum interfraction interval of 8 hours (mean interfraction interval, 12 h). In one patient, the prescribed dose of 2100 cGy was delivered in two fractions because of a technical error in dose calculation discovered at the completion of the first fraction. One patient experienced severe claustrophobia-like symptoms attributable to the stereotactic frame and was given the third and final treatment 5 hours after the second fraction. No patient was lost to follow-up. There were two deaths: one patient died from complications of multiple sclerosis, and a second patient, with advanced NF2, died from postoperative

complications after surgical resection of a 5-cm contralateral VS. The minimum, median, and maximum clinical follow-up intervals for the 31 surviving patients are 0.5, 2, and 4 years, respectively.

Tumor control

Radiographic follow-up was available for all surviving patients (32 tumors) (Fig. 1). Twenty-two (85%) of 26 tumors had a significant loss of central contrast enhancement on the patients' 6-month follow-up MRI scans. Tumor regression was documented in 11 patients (34%), tumor stabilization in 20 (63%), and tumor progression in 1 (3%). The actuarial probability of freedom from tumor progression at 2 years was 93% (Fig. 2). In the one patient with tumor progression, growth of an NF2-associated VS was observed 1.8 years after SRS. This patient was assessed frequently during the next 2 years, during which time no further growth occurred and subsequent tumor regression was observed. During this continued observation period, the patient remained asymptomatic and did not require surgical intervention.

Trigeminal and facial nerve injury

Five patients (16%) developed trigeminal nerve injury at a median of 6 months (range, 4–12 mo) after SRS. Three of these patients had no preexisting trigeminal symptoms. One patient experienced worsening of a preexisting trigeminal dysesthesia. One patient with preexisting trigeminal neuralgia experienced a severe case of ipsilateral herpes zoster 3 months after SRS and developed anesthesia of the affected trigeminal branches. One

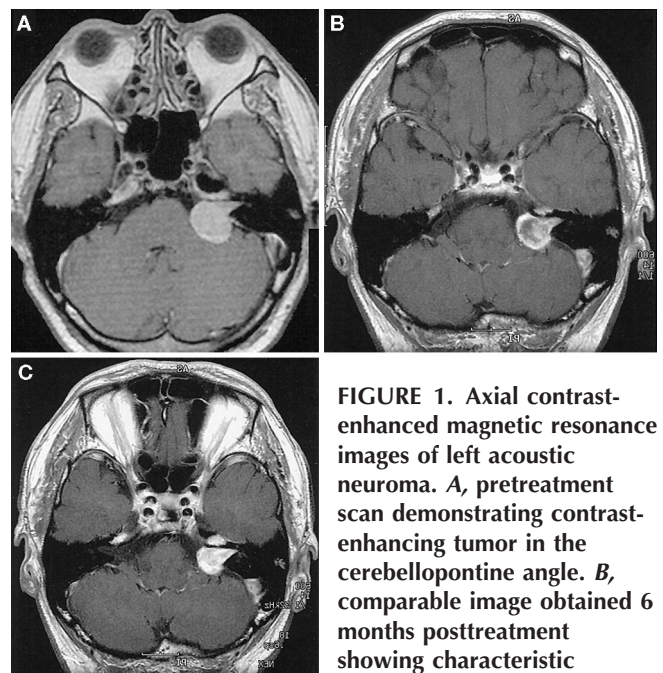


FIGURE 1. Axial contrast-enhanced magnetic resonance images of left acoustic neuroma. **A**, pretreatment scan demonstrating contrast-enhancing tumor in the cerebellopontine angle. **B**, comparable image obtained 6 months posttreatment showing characteristic decreased central contrast enhancement. **C**, image obtained 18 months posttreatment showing a decrease in the tumor size and recovery of some contrast enhancement.

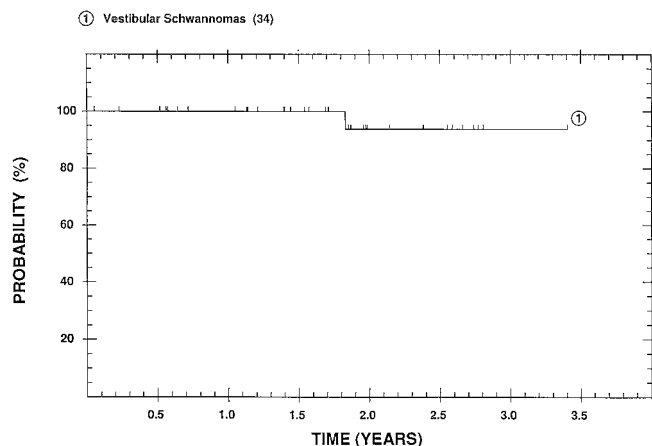


FIGURE 2. Actuarial freedom from tumor progression.

patient (3%) developed a facial nerve injury (House-Brackmann Grade III) 7 months after SRS. The injury persisted at this level 7 months after onset. All other patients (97%) maintained House-Brackmann Grade I to II facial function at the last follow-up examination. Two patients experienced transient vertigo. There have been no other treatment-related complications. There were no statistically significant associations between cranial nerve injury and any of the patient, tumor, or treatment characteristics. Tumor size greater than 20 mm was associated with a trend toward greater risk of trigeminal nerve injury (28% versus 6%; $P = 0.16$) (Fig. 3).

Hearing preservation

For most patients, functional hearing as measured by PTA, speech reception threshold, and speech discrimination diminished gradually throughout the follow-up period. The average increase in PTA or speech reception threshold was 9, 14, and 18 dB at 1, 2, and 3 years, respectively. For all patients with serviceable hearing before treatment (GR Class 1–3), the

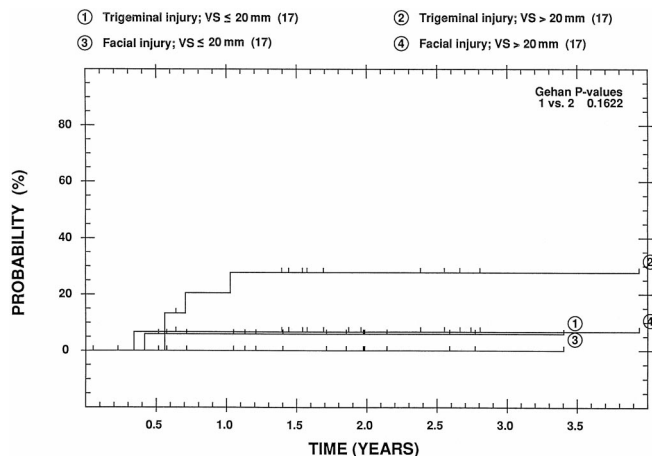


FIGURE 3. Actuarial trigeminal and facial nerve complications for tumors 20 mm or smaller compared with tumors larger than 20 mm.

actuarial probability of retained serviceable hearing at 2 years was 81%. All patients with pretreatment Class 1 to 2 hearing ($n = 13$) maintained serviceable (Class 1–3) hearing at a median follow-up period of 2 years, and only four (50%) of eight patients with pretreatment Class 3 hearing maintained Class 1 to 3 hearing ($P = 0.007$) (Fig. 4). If only “useful” hearing (Grade I–II) is considered, 77% of patients maintained this level. Univariate analysis demonstrated that the presence of NF2 was the only other factor associated with poorer hearing preservation. The rates of preservation of serviceable hearing at 2 years were 92% and 67% for sporadic and NF2 patients, respectively ($P = 0.15$).

DISCUSSION

An intimate anatomic relationship exists among the trigeminal, facial, and vestibulocochlear nerves and the cerebellopontine angle schwannoma that places these nerves in jeopardy during either microsurgical resection or stereotactic radiosurgery. Identification of the range of anatomic variance and general refinement in microsurgical and radiosurgical techniques have substantially improved outcomes for patients with VS. Most modern surgical and SRS series report complete tumor removal (microsurgery) or cessation of growth (radiosurgery) with anatomic and physiological preservation of facial nerve function in 90% of patients (4, 7, 16, 24, 26, 33–35, 39, 41). Preservation of cochlear nerve function with useful or serviceable hearing has presented a significantly greater challenge. The probability of preserved useful hearing has ranged from 30 to 50% with either technique and may be considerably lower for larger tumors (7, 10–12, 14–16, 18, 21, 23, 25, 33, 41, 42). Surgical transection and devascularization, delayed postoperative fibrosis (40), postradiation edema (6), Schwann cell radiation injury, and radiation vascular injury (3, 28) have been implicated as potential mechanisms for acute or delayed cochlear nerve injury.

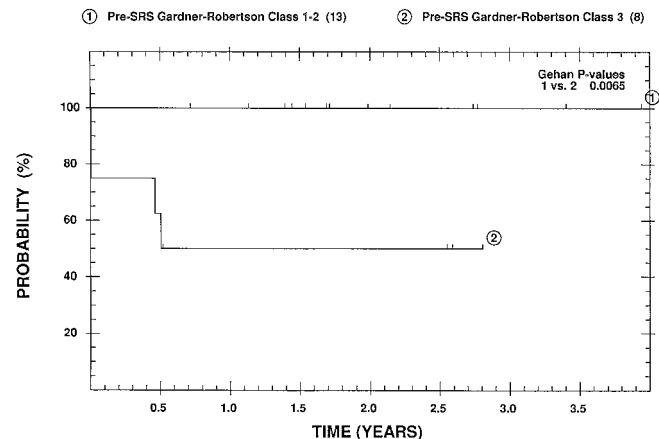


FIGURE 4. Preservation of serviceable hearing for patients with good pretreatment hearing (GR Class 1–2) compared with patients with marginal pretreatment hearing (GR Class 3).

Rationale for fractionated SRS

The efficacy of SRS in the treatment of intracranial tumors ultimately depends on the inherent sensitivity of the tumor relative to the tolerance of adjacent neural structures. It is well established in conventional radiation therapy that both tumor sensitivity and normal tissue tolerance can be improved with fractionated treatment. Fundamental radiobiological principles predict that fractionated radiotherapy (the delivery of the total radiation dose in several smaller increments over a period of time) allows for preferential repair of sublethal damage in normal tissues, reoxygenation of hypoxic tumor cells, and redistribution of surviving tumor cells into a more radiosensitive cell cycle phase. The summation of these effects causes a separation of the tissue injury thresholds of normal and neoplastic tissues, thereby enhancing the therapeutic index. Although there are no experimental studies specifically designed to assess the biological effects of fractionated SRS in human VS, preclinical and clinical data exist to support the hypothesis of reduced neural injury with fractionation of the radiation dose. The optic chiasm is the classic example, in which injury may be observed after a single-fraction radiosurgery dose of 1000 cGy, although 5000 cGy administered during a 5-week interval with conventional fractionation is well tolerated (20).

The optimal fractionation schedule in SRS for VS is not known, and few useful clinical data exist. In vitro studies with human tissue cell lines suggest that repair of sublethal radiation damage occurs relatively rapidly, with a half-time of 30 minutes (5). In vivo studies of the rat spinal cord support a slower mechanism for repair, with a half-time of approximately 4 hours (2). Using the more conservative half-time estimate of 4 hours, one can predict that 80 to 90% of sublethal injury recovery occurs during interfraction intervals of 10 to 14 hours. This estimate provided the rationale for the fractionation schedule used in our protocol. In developing our treatment strategy, we sought to preserve the accuracy of a rigid fixation system and the practicality of a brief treatment regimen. We designed a schedule consisting of three fractions of 700 cGy, administered during a 24-hour period, allowing interfraction intervals of 10 and 14 hours. By restricting the fractionation to three doses, the use of multiple isocenters to achieve dose conformality remained practical within the time constraints of a nondedicated medical linear accelerator. The total dose of 2100 cGy was estimated to be biologically equivalent to a conventional fraction dose of 4700 to 6300 cGy (linear quadratic formula assuming an α/β of 1–2) or a single-fraction SRS dose of 1400 to 1500 cGy (5).

Tumor control and complications

Preliminary results from this series compare favorably with those of single-fraction SRS. Our 2-year tumor control (93%) and trigeminal nerve injury (16%) rates are similar to those observed at 4 years by the University of Pittsburgh (97% and 23%, respectively) (9) and by the University of Florida (100% and 19%, respectively) (30). The most recently published results imply both durability of tumor control (98%) and stability of trigeminal nerve function at 5 to 10 years of follow-up

(24). We have observed only one patient (3%) with facial nerve injury (House-Brackmann Grade III) of 31 assessable patients, a slightly lower rate of injury than observed at the University of Pittsburgh (17%) and the University of Florida (16%).

Hearing preservation

Comparisons of hearing preservation rates among published clinical series are more difficult because of a variety of definitions for “useful” and “serviceable” hearing and differences in referral patterns across institutions. At the University of Pittsburgh, serviceable hearing (defined there as a pretreatment GR Class 1–2) was present before treatment in 63 of 273 patients receiving single-fraction SRS. Three years after radiosurgery, 30 (48%) of 63 patients maintained serviceable hearing (8). In contrast, nearly all patients referred to the University of Florida had no useful hearing in the affected ear before SRS, and routine audiometric assessments were not performed (31). The present series is unique in that a large percentage of patients (30%) had NF2 and eight of these patients had no hearing in the contralateral ear. In our experience, patients with contralateral deafness consider any measure of preserved hearing useful and generally have serviceable hearing with PTAs (or speech reception thresholds) greater than 50 dB (GR Class 3). For these reasons, we have avoided the term “useful” hearing and have designated GR Class 1 to 3 as “serviceable” to recognize a range of hearing usefulness within the Class 3 designation. All patients with good (Class 1–2) pretreatment hearing who were treated on this protocol maintained GR Class 1 to 3 hearing. In contrast, only 50% of patients in this study with Class 3 hearing pretreatment maintained serviceable hearing (one patient improved to Class 2, and three maintained Class 3), and 50% had no measurable hearing within 1 year of SRS. This suggests an advantage with early intervention. The preservation rates of serviceable hearing at 2 years were 92% and 67% for sporadic and NF2 patients, respectively. Given the inherent difficulty of surgically separating the embedded VIIIth cranial nerve from the tumors associated with NF2 (17, 29), hearing preservation in two-thirds of patients with NF2, most of whom were deaf in the contralateral ear, may be the most significant potential advantage of fractionated SRS.

In contrast to our decision to define serviceable hearing as Grades 1 to 3, prior studies have defined useful hearing as only Grades 1 to 2. For comparison, 10 (77%) of 13 patients in our study maintained this level of hearing. This compares favorably with recent published results. The University of Pittsburgh group demonstrated an increase in preservation of Class 1 and 2 hearing of 40 to 56% after dose reduction and implementation of magnetic resonance targeting (8). Another study did not include sufficient numbers of patients in the lower-dose group to assess improvement in hearing preservation, which was 39% overall (Class 1–2) (32). As with fractionation, the long-term effect of dose reduction on tumor control is unknown.

Another method for assessing cochlear nerve injury using purely objective criteria is the measurement of PTA or speech

reception threshold before and after SRS. Hirsch and Noren (18) reported the audiological findings after single-fraction SRS for VS from the experience at the Karolinska Institute in Stockholm and noted average hearing losses of 22, 27, and 32 dB at 1, 2, and 3 years, compared with PTA pretreatment values. In contrast, patients treated with fractionated SRS in the present study experienced average hearing losses of 9, 14, and 18 dB during the same time intervals (Fig. 5). Given the limitations of this type of comparison, the suggestion of an approximately 50% reduction in cochlear nerve injury with fractionated treatment is noteworthy.

Two other SRS centers have adopted fractionated radiosurgery to manage VS. Varlotto et al. (43) at Harvard University have used conventionally fractionated SRS with a relocatable Gill-Thomas-Cosman III stereotactic frame in eight newly diagnosed and four recurrent tumors. These patients, with relatively large tumors (median tumor volume, 10.1 cm³), received 5040 cGy in 30 daily fractions during 6 weeks. After a median follow-up period of 2.2 years, all lesions were controlled with no cranial nerve injuries, and useful hearing was preserved in all nine patients who had good pretreatment hearing. Lederman et al. (27) used a similar relocatable radiosurgical technique in a more abbreviated treatment schedule for 33 patients with VS treated at the Staten Island University Hospital. All patients received 2000 cGy in four or five daily fractions during 1 week. With a median follow-up of 2 years, all tumors were controlled and no new cranial nerve injuries were observed. Of 28 patients with audiometric assessments, 90% had stable or improved hearing at their last follow-up examination. Both of these centers report excellent 2-year results with all tumors controlled, no significant cranial nerve injuries, and good to excellent preservation of hearing. Although these data support the concept that fractionation provides an opportunity for tumor control with reduced neuronal injury, they do not demonstrate a clear advantage of more protracted schedules. For patients with a tumor 20 mm or smaller and good pretreatment hearing, a 1-day fractionated

SRS program seems to achieve results comparable to those attained with SRS schedules requiring 1 to 6 weeks.

CONCLUSION

The two accepted treatments for VS (microsurgery and SRS) are both associated with substantial risk of injury to the cochlear nerve and relatively low rates of functional hearing preservation. Although some SRS centers have addressed this problem by reducing the single-fraction radiosurgery dose, others have adopted removable stereotactic systems and extended fractionation schedules. Our experimental approach was designed to combine the precision of skeletal fixation and the practicality of a 1-day treatment with an abbreviated SRS fractionation schedule. After 4 years, we have sufficient follow-up data to report treatment-related complications and actuarial rates of hearing preservation, both of which compare favorably with microsurgery and single-fraction radiosurgery. Although our tumor control rates are comparable to those reported in other SRS series, the long natural history of VS necessitates longer follow-up to assess the durability of tumor control.

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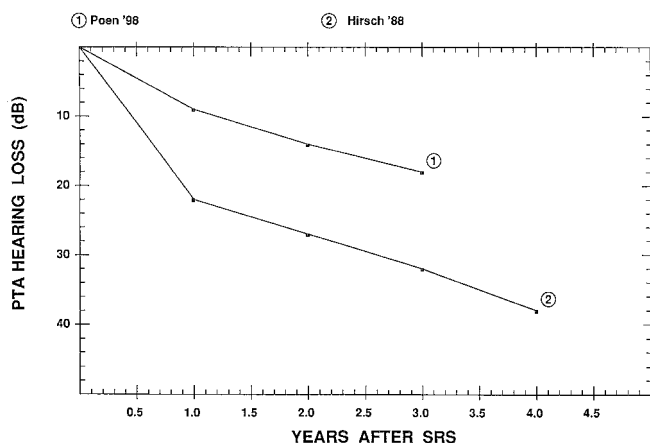


FIGURE 5. Hearing loss (PTA after SRS compared with pretreatment levels) over time in the present series compared with the single-fraction gamma knife experience of Hirsch and Noren (18) in Stockholm.

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COMMENTS

The authors and several other groups are beginning to fractionate radiosurgical doses in an attempt to reduce cranial nerve complications. In doing so, they risk inferior tumor control because fractionation will reduce the biological effect on the tumor as well as on the normal tissue. The authors invoke postirradiation cell cycle reassortment and reoxygenation as factors enhancing tumor cell kill with fractionation; however, even if these factors occur in schwannomas, which is speculative, they are far weaker than the tumor-sparing effect of postirradiation sublethal damage repair allowed by the intervals between doses.

Preservation of hearing and facial nerve function as reported here may be slightly better than the University of Pittsburgh experience with single-fraction gamma knife treat-

ment of acoustic tumors (1), but this series is smaller and has a shorter follow-up period. It is reasonable to think that fractionation will have a propitious effect on normal tissue, but critical information on comparable efficacy awaits further follow-up.

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Poen et al. report their initial 2-year experience in patients treated with "fractionated radiosurgery." In this particular instance, I have less argument with the concept of fractionated radiosurgery because the patient was treated during a 24-hour period. The authors used frame-based linear accelerator radiosurgery, for which the frame remained attached to the patient's head during the delivery of three 700-cGy fractions. The authors compare their results with rather outdated literature. During the last 5 years, dose reduction, magnetic resonance imaging targeting techniques, and improved conformal plans (an average of 7–10 isocenters per patient using small beam diameters) have significantly improved results at many sites where gamma knife radiosurgery is performed. It is estimated that in the year 2000, more than half of annually diagnosed acoustic neuroma patients will undergo radiosurgery as the primary treatment modality. This statistic reveals the significant impact of new technologies in the management of a rare tumor. The authors have used this technique effectively, but the need for fractionation is inversely related to the conformality of the treatment plan. The less conformal the treatment plan, the more fractions must be administered to reduce the dose to adjacent structures. Although the authors quote the radiation therapy mantra on the reasons for fractionation (reoxygenation, repair, redistribution), there is surprisingly little fundamental radiobiological evidence to support these concepts. A slow-growing benign brain tumor has a cell cycle time not greatly different from cell cycle times in the surrounding brain. In this case, the mechanism of radiosurgical action is the creation of inalterable DNA damage that is not recognized until the cell attempts division, at which point it probably becomes apoptotic. In addition, a secondary vascular effect from radiosurgery results in an additional cumulative benefit by obliteration of the intratumoral vasculature. This leads to hyalinization and fibrosis within the tumor.

This technique, as well as true radiosurgery, must be significantly differentiated from the use of relocatable stereotactic frames to achieve abbreviated treatment schedules in patients with vestibular schwannomas. The results of fractionated radiation have yet to be reviewed in any significant way.

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Poen et al. treated 31 patients with acoustic schwannomas with a hypofractionated course (three fractions in 20 h) of stereotactic radiosurgery. Three doses of 700 cGy were delivered, for a total peripheral dose of 2100 cGy. With a median follow-up of 2 years, 97% tumor control was demonstrated. Five patients developed trigeminal nerve injury. One patient developed a facial nerve injury. Preservation of serviceable hearing was 81% at 2 years.

As the authors point out, these are preliminary data. One suspects that tumor control and hearing preservation will decline as median follow-up time increases. Nonetheless, they have carefully studied and reported a completely new fractionation protocol for acoustic schwannomas. This protocol is much more convenient than conventional fractionation (30 fractions), but it may still take advantage of some of the normal tissue-sparing effects that are lost in single-fraction radiosurgery.

The debate about fractionation versus single-fraction radiosurgery for acoustic schwannomas is unresolved. Unfortunately, the debate is clouded by reports of single-fraction results using inaccurate radiation delivery, computed tomographic dose planning only, poorly conformal dose planning, or doses that are now known to be too high. Along with the University of Pittsburgh, our group thinks that single-fraction treatment, delivered with magnetic resonance imaging, modern highly conformal dose planning, and at lower doses (1000–1250 cGy) than originally recommended, is the best choice. Using this approach, we expect tumor control and hearing preservation rates similar to those reported by the authors. In addition, the incidence of trigeminal neuropathy is expected to be much lower.

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The number of reports on radiosurgical treatment of vestibular schwannomas by gamma knife or linear accelerator is increasing. However, few note improved hearing preservation as a major goal. In 31 of 32 patients, the authors report stable tumor size at 6 months to 4 years after fractionated radiosurgery. Of previously hearing patients, 81% retained some hearing at Gardner-Robertson Class 1 to 3. The authors present their new protocol of fractionated radiosurgery performed in three applications within 24 hours. These early results seem comparable to those obtained using gamma knife surgery for tumor control and cranial nerve morbidity.

The problem of cranial nerve morbidity deserves special consideration. Vestibular function is rarely reported or possibly receives little consideration in radiotherapy. Especially in small tumors with a predominantly vestibular presentation, persistent recurrence of vestibular disturbances poses a problem. The incidence of trigeminal nerve neuropathy is considerable in all radiosurgical reports to date (1, 2, 5), with very rare exceptions (3), and it severely compromises life quality. Trigeminal disturbance before treatment is a completely different matter in vestibular schwannomas, because nerve integrity is not usually endangered by the microsurgical process. Rather, it is improved by decompression from the tumor

with reversibility of symptoms. Trigeminal neuropathy *after* application of radiosurgery is a serious lesion, and a cure is virtually impossible. Its effects include postradiotherapeutic onset of burning, dysesthesia, and corneal problems that cannot be reliably treated surgically or medically. This is a serious and highly underestimated morbidity.

Preservation of auditory function is reported at promising levels and rates. Still, as learned from previous experience, hearing stability is not obtained during the 1st or 2nd year after radiosurgery. Therefore, a judgment on the reliability of hearing preservation and the stability of tumor control is impossible for the treatment protocol presented.

Patients with neurofibromatosis Type 2 (NF2) pose a special challenge in making the right treatment decision at the right time. In our series of 195 patients with NF2, hearing could be preserved in 35% of operated ears. In a trial of hearing preservation in the last hearing ear, subtotal tumor resection and decompression of the internal auditory canal succeeded in preserving hearing in 15 patients; tumor regrowth has been moderate and has not necessitated reoperation. None of the patients so treated lost hearing during the follow-up period. Furthermore, preserved hearing has remained serviceable for periods up to 12 years. In the case of a secondary hearing loss at tumor recurrence many years later, this concept fully preserves the option of placing an auditory brainstem implant. Therefore, this treatment program seems more suited to the difficult situation of NF2 patients and avoids the possible risk of malignant tumor formation (4). Profound knowledge of the variability in NF2 disease courses and individual patient histories is essential to patient selection for this mode of treatment.

The authors' attempts to develop a protocol focusing on function protection should be acknowledged. A radiosurgery protocol with fractionated treatment as an option for patients who cannot undergo surgery, but who need tumor reduction, would be most welcome. Nonetheless, we must be aware that these and similar trials are currently performed in high num-

bers without the ability to foresee the long-term effects and possible problems. Some patients who would have had a realistic chance for long-term definitive cure *and* functional cranial nerve preservation by microsurgery will experience an increasing hearing loss without any chance of surgical interference. Some patients will need surgery at a later stage; this surgery is more difficult and hazardous and bears a reduced chance for functional facial nerve preservation (statistically, 1 of 3 patients). Clinically and scientifically, the most critical point is the current lack of communication among specialists. The surgeons who will be confronted with these patients at a later stage are not consulted by the radiosurgeons at the time the initial treatment decision is made. Teaching and handling this difficult surgery is not sufficiently discussed among colleagues.

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