Staged Stereotactic Irradiation for Acoustic Neuroma

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OBJECTIVE: Stereotactic radiosurgery has proven effective in the treatment of acoustic neuromas. Prior reports using single-stage radiosurgery consistently have shown excellent tumor control, but only up to a 50 to 73% likelihood of maintaining hearing at pretreatment levels. Staged, frame-based radiosurgery using 12-hour interfraction intervals previously has been shown by our group to achieve excellent tumor control while increasing the rate of hearing preservation at 2 years to 77%. The arrival of CyberKnife (Accuray, Inc., Sunnyvale, CA) image-guided radiosurgery now makes it more practical to treat acoustic neuroma with a staged approach. We hypothesize that such factors may further minimize injury of adjacent cranial nerves. In this retrospective study, we report our experience with staged radiosurgery for managing acoustic neuromas.

METHODS: Since 1999, the CyberKnife has been used to treat more than 270 patients with acoustic neuroma at Stanford University. Sixty-one of these patients have now been followed up for a minimum of 36 months and form the basis for the present clinical investigation. Among the treated patients, the mean transverse tumor diameter was 18.5 mm, whereas the total marginal dose was either 18 or 21 Gy using three 6- or 7-Gy fractions. Audiograms and magnetic resonance imaging were obtained at 6-months intervals after treatment for the first 2 years and then annually thereafter.

RESULTS: Of the 61 patients with a minimum of 36 months of follow-up (mean, 48 mo), 74% of patients with serviceable hearing (Gardner-Robinson Class 1–2) maintained serviceable hearing at the last follow-up, and no patient with at least some hearing before treatment lost all hearing on the treated side. Only one treated tumor (2%) progressed after radiosurgery; 29 (48%) of 61 decreased in size and 31 (50%) of the 61 tumors were stable. In no patients did new trigeminal dysfunction develop, nor did any patient experience permanent injury to their facial nerve; two patients experienced transient facial twitching that resolved in 3 to 5 months.

CONCLUSION: Although still preliminary, these results indicate that improved tumor dose homogeneity and a staged treatment regimen may improve hearing preservation in acoustic neuroma patients undergoing stereotactic radiosurgery.

KEY WORDS: Acoustic neuroma, CyberKnife, Hearing preservation, Image guidance, Radiosurgery

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Stereotactic radiosurgery has been used for decades to treat acoustic neuromas, and a growing body of literature supports both the safety and efficacy of this treatment (4, 13–17, 23, 25, 26, 28, 30, 36, 37, 39–41, 44, 46, 47, 50, 51, 58, 59, 62). These prior studies repeatedly have demonstrated stereotactic radiosurgery to be an effective alternative to microsurgical resection for small to medium tumors, with rates of tumor control that range from 92 to 100% (13, 16, 23, 28, 30, 36, 41, 44, 58, 59, 62). The likelihood of hearing preservation in earlier clinical series was noted to be 51 to 60% (25, 26, 28, 30, 36, 41), but more recent studies in which more isocenters were used to enhance conformal treatment suggest that intermediate-term hearing preservation rates can be improved to between 71 and 73% (13, 46, 58). Despite such recent progress, there continues to be a significant number of patients with acoustic neuroma for whom hearing worsens after radiosurgery, including a report of neurofibromatosis Type II patients with acute hearing loss (7). Further reducing the likelihood of such deterioration continues to represent a major challenge.

A large radiobiological literature forcefully argues that injury to adjacent normal cranial nerves may be mitigated in part by fractionating or staging a course of treatment into a series of smaller doses of radiation (12, 33, 38, 67). With these radiobiological principles in mind, a number of recent clinical studies have investigated the advantages of fractionation for treating acoustic neuroma (1, 2, 5, 18, 19, 43, 48, 59, 61, 65–68). The two basic alternative strategies that have been used to date involve either staged, frame-based radiosurgery or conventionally fractionated radiotherapy.

Staged radiosurgery using the gold standard of a skeletally attached stereotactic frame is possible, but generally not practical, especially if an interfraction interval of 24 hours is to be used. Such a course of treatment necessitates that a patient wear a stereotactic frame continuously over several consecutive days, a not inconsequential feat of endurance. As an alternative, standard radiotherapy, involving up to 30 fractions, has also been used to treat acoustic neuromas (5, 18, 19, 61). The relative reduction in accuracy and conformality compared with radiosurgery methods is a principle drawback to this approach. Even with the most precise techniques for external beam radiation therapy set-up, such as relocatable head frames (e.g., the Gill-Thomas-Cosman system), the targeting of radiation is less accurate than that which can be achieved with frame-based radiosurgical methods. An exception is the relocatable Zmed head device (Varian Medical Systems, Inc., Palo Alto, CA), which in dentate patients has accuracy comparable with that of stereotactic frames (52).

The recent availability of image-guided robotic radiosurgery now makes it possible to deliver multiple sessions of highly conformal radiation to lesions with an application accuracy that equals that of conventional stereotactic frames (6). The combination of relative accuracy, conformality, and the frameless nature of this system makes it readily feasible to treat intracranial tumors with staged radiosurgery. These advances formed the basis for treating selected acoustic neuromas with staged CyberKnife (Accuray, Inc., Sunnyvale, CA) radiosurgery at Stanford University Medical Center beginning in 1999. Before that date, patients undergoing staged radiosurgery for acoustic neuromas at Stanford were treated with a less practical frame-based radiosurgery system, the results of which have been reported previously (48). We believe our current method of radiosurgery is an improvement over our prior frame-based technique in that patients are no longer hospitalized for the duration of a 36-hour treatment.

PATIENTS AND METHODS

Patient Population

Between 1999 and 2001, 61 patients with unilateral acoustic neuromas were treated at Stanford University School of Medicine using stereotactic radiosurgery delivered in three stages. The Stanford University Institutional Review Board approved the prospective and retrospective collection of data for this cohort of patients. Among this group there were 29 men (49%) and 32 women. Mean patient age was 54 years (range, 27–79 yr). Thirty-one (51%) of the 61 acoustic neuromas were located on the right side and 30 were located on the left. Among the eight patients (13%) in whom there had been a prior surgical resection, either residual tumor was detected on postoperative imaging or a new postsurgical tumor recurrence subsequently developed on follow-up imaging. None of the patients reported here had a diagnosis of neurofibromatosis Type II. All patients receiving radiosurgery for their acoustic neuroma during this period were treated with the protocol outlined in this article.

Tumor Size and Measurements

Pretreatment magnetic resonance imaging (MRI) was obtained within 3 months of radiosurgery for all patients. Tumors were measured in three orthogonal dimensions. The intracanalicular component of the tumor was included in the maximal transverse diameter when calculating measurements. The mean pretreatment maximal tumor dimension was 18.5 mm (range, 5–32 mm).

Audiograms

Baseline pretreatment audiograms were obtained within 3 months of radiosurgery in all patients except for those with no hearing in the involved ear as demonstrated on a prior audiological test. Speech reception threshold in decibels, speech discrimination levels in decibels, and pure tone average were recorded.

Cranial Nerve Grading

Preoperative and postoperative evaluation of cranial nerves V, VII, and VIII were performed. Hearing was graded before and after treatment according to the Gardner-Robertson classification system (20). Thirteen patients demonstrated Gardner-Robertson Grade 5 on the treated side before radiosurgery. Facial nerve function was rated according to the House-Brackmann grading system (27). Trigeminal nerve function was graded according to a semiquantitative scale as normal sensation, decreased sensation, or no sensation. Both transient and permanent cranial nerve deficits were noted.

Radiosurgery Technique

After comfortably positioning each patient supine on the CyberKnife treatment table, a custom Aquaplast (WFR/Aquaplast Corp., Wyckoff, NJ) mask was fabricated. While the patient was immobilized in the mask, with a thin foam pad used behind the head when necessary for comfort, a thin-slice (1.25 mm) high-resolution computed tomographic (CT) scan was obtained with a GE Light Speed 8i Scanner (Milwaukee, WI) after the intravenous administration of 125 ml of Omnipaque contrast (iohexol, 350 mg I/ml; Nycomed, Inc., Princeton, NJ). The acquired images were transferred by network to the CyberKnife treatment planning workstation. Tumor volumes and critical structures (brainstem) were delineated manually by the treating surgeon on axial images with simultaneous overlay of the outlines on coronal and sagittal reconstructions. In our experience, high-resolution thin-slice contrast CT images made with modern multidetector scanners (8 slice or 16 slice) permit the detailed visualization of nearly all acoustic neuromas. However, in the rare instance where CT images were not optimal, such as small volume tumors or tumors in which the intracanalicular portion of the tumor did not fill the entire canal based on pretreatment MRI, a CT/MRI fusion was performed. In these cases, a thin-section contrast MRI scan was fused to the treatment planning CT scan using the commercially available fusion software provided with the CyberKnife. MRI was used to help delineate the tumor boundary. A CT scan is necessary in every patient to provide the skeletal anatomy that the CyberKnife uses for real-time patient tracking during treatment.

Nonisocentric, inverse planning helped to achieve a maximally conformal radiosurgical dose while minimizing the dose to the brainstem. When using inverse planning, the physician inputs specific treatment criteria, and in an iterative fashion, the CyberKnife planning algorithm computes a series of conformal radiosurgical plans (1). Dose volume histograms that were calculated for the target region and nearby critical structures were used to evaluate and select the best treatment plan. Total treatment dose was 21 Gy for the first 14 patients, based on our prior experience with frame-based staged stereotactic irradiation of acoustic neuromas; this dose originally was selected on the basis of a radiobiological equivalence to a single 14-Gy dose (48). Because of the excellent rate of tumor control among these initial patients and widespread published evidence that a decreased single fraction size was equally efficacious, we decided to lower the total dose to 18 Gy for the remaining 47 patients in this series. This change was introduced in an attempt to further improve the rate of posttreatment hearing preservation. In every patient, the total dose of radiation was divided into three equal doses delivered in consecutive daily stages separated by approximately 24 hours. Eight milligrams of dexamethasone was administered orally after each stage of treatment.

Clinical and Radiographic Follow-up

For the first 2 years after radiosurgery, radiographic follow-up was performed using 2- to 3-mm slice thickness gadolinium-enhanced MRI every 6 months. MRI was repeated annually thereafter. Orthogonal tumor dimensions, as described above, were recorded from follow-up images on a prospective basis. With the exception of the 13 patients who had Gardner-Robertson Grade 5 hearing before treatment, audiograms also were obtained every 6 months for the first 2 years after treatment, and then annually thereafter. Whenever possible, patients obtained follow-up audiograms at the same diagnostic center to minimize differences in technique.

Clinical follow-up, which includes detailed neurological examination and testing of cranial nerves V, VII, and VIII, was obtained every 6 months for the first 2 years and then annually thereafter. Mean clinical and radiographic follow-up was 48 months (range, 36–62 mo).

RESULTS

Radiographic Tumor Response

Tumor size was measured on each follow-up MRI scan and compared with pretreatment measurements. For the overall series, 29 (48%) of 61 tumors decreased in size, and 31 tumors (50%) were stable, producing a tumor control rate of 98% (*Fig. 1*). One patient with an acoustic neuroma was noted to have an increase in tumor size 4 years after treatment, and this patient subsequently underwent surgical resection. The loss of central contrast enhancement within the treated lesion was observed routinely on MRI at 6 to 12 months after radiosurgery, but it did not correlate with tumor shrinkage.

Hearing Preservation

The mean follow-up period for hearing assessment was 48 months (range, 36–62 mo). Of the 61 patients in this series, 13 patients had no measurable hearing (Gardner-Robertson Grade 5) and were not tested with serial audiograms after treatment. Of the remaining 48 patients, all had Gardner-Robertson Grade 1 to 3 hearing before treatment. Forty-three

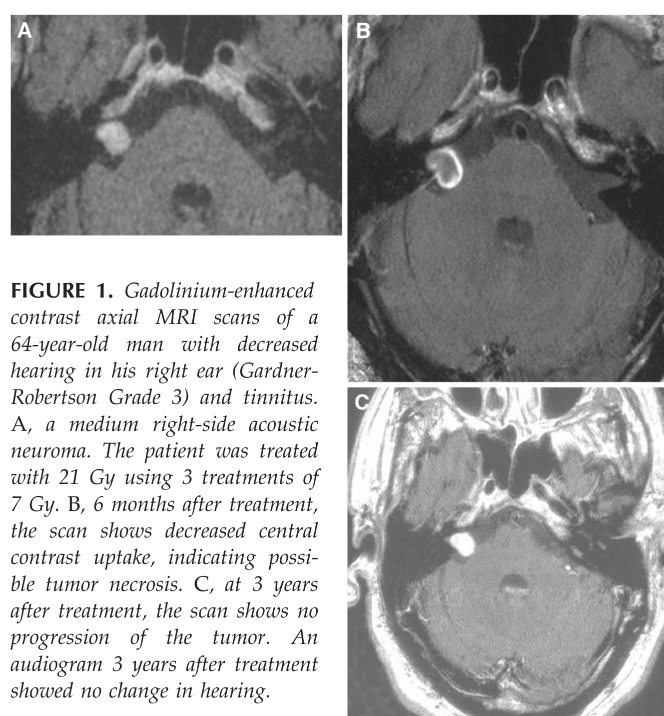

FIGURE 1. *Gadolinium-enhanced contrast axial MRI scans of a 64-year-old man with decreased hearing in his right ear (Gardner-Robertson Grade 3) and tinnitus.* A, *a medium right-side acoustic neuroma. The patient was treated with 21 Gy using 3 treatments of 7 Gy.* B, *6 months after treatment, the scan shows decreased central contrast uptake, indicating possible tumor necrosis.* C, *at 3 years after treatment, the scan shows no progression of the tumor. An audiogram 3 years after treatment showed no change in hearing.*

(90%) of these patients maintained Gardner-Robertson Grade 1 to 3 hearing at last follow-up. Of the 35 patients with Gardner-Robertson Grade 1 to 2 hearing as measured on audiogram before treatment, 26 (74%) of these patients maintained this same level of hearing at last follow-up. Two patients (4%) had an improvement in their Gardner-Robertson grade, with one patient improving from Grade 2 to Grade 1 and the second patient improving from Grade 3 to Grade 1. A summary of pretreatment and posttreatment pure tone averages and speech discrimination scores is shown in *Table 1*.

Facial Nerve Deficits

Facial nerve function was graded according to the House-Brackmann scale (27) at each clinical follow-up examination. None of the patients treated in this series experienced new facial weakness. One patient had House-Brackmann Grade 3 weakness before radiosurgery as a result of previous subtotal resection of her tumor, and there was no change in her facial nerve function after radiosurgery. Two patients experienced transient facial twitching during the first 12 months after treatment, but the symptoms resolved in 3 months in one patient and in 5 months in the other.

Trigeminal Nerve Deficits

Trigeminal nerve deficits typically are associated with larger acoustic neuromas. Smaller lesions, and especially intracanalicular tumors, are relatively distant from the trigeminal nerve. However, in this series, no patients with acoustic neuromas of any size developed trigeminal nerve symptoms after treatment.

Other Complications

Symptomatic brainstem or cerebellar edema was noted in one patient during the first 12 months after treatment. This patient previously had undergone resection of a large right-sided acoustic neuroma 15 years previously. His immediate preradiosurgery MRI scan showed a 3.2-cm recurrence (the largest tumor in this series) that was treated with 18 Gy of radiation. Five months after radiosurgery, the patient experienced left lower extremity sensory loss that fully resolved over the next 3 months. Brain MRI at that time showed a T2 signal change along the lateral brainstem. These abnormalities resolved fully on subsequent imaging studies.

TABLE 1. Summary of pure tone averages and speech discrimination scores before treatment and at the last posttreatment follow-up

	Before treatment	After treatment	*P* value
Pure tone average (dB)	34.9	48.8	<0.001
Speech discrimination score (%)	72.2	60.6	0.011

DISCUSSION

Microsurgical Options for Acoustic Neuromas

Contemporary surgical options for acoustic neuroma include microsurgical resection by means of either a retromastoid, subtemporal, or translabyrinthine approach (53, 56, 63). Even in the most experienced hands, hearing and facial nerve preservation represent an ongoing operative challenge, especially for larger tumors (i.e., >2 cm) (21). Sampath et al. (54) reported that after microsurgical resection of acoustic neuromas smaller than 2.5 cm, normal facial nerve function was retained in only 60.8% of patients. Several other conventional operative series have documented the importance of neuroma size in determining the risk of facial nerve injury after microsurgical resection of acoustic neuroma (3, 10, 22, 32, 64). With regard to hearing preservation, acoustic neuroma size again predicts outcome. Hecht et al. (24) reported in a series of 60 patients that hearing preservation was only 16% for tumors more than 1.5 cm and 50% for tumors less than 1.5 cm. This finding has been confirmed by others (8, 9, 11, 21, 29). The mere existence of the commonly used translabyrinthine approach for removing larger lesions, which by design sacrifices all ipsilateral residual hearing, provides ample evidence that hearing preservation with present day operative methods is far from ideal.

Rationale for Irradiating Acoustic Neuroma

Because of the not inconsequential potential for cranial nerve morbidity after microsurgery, stereotactic radiosurgery has emerged as a viable treatment alternative for small to medium acoustic neuromas. Initial radiosurgical studies beginning almost 2 decades ago focused on tumor control. However, as it became clear that control rates were very high, subsequent efforts have focused on minimizing cranial nerve morbidity. Ultimately, the protection of residual hearing has been the goal of most recent technical refinements in radiosurgical treatment. This especially holds true for patients with medium acoustic neuromas (1.5–2.5 cm), a group in whom hearing preservation after microsurgical resection remains inadequate.

Comparing Irradiation Methods for Acoustic Neuroma

Multiple publications have reported outcomes after stereotactic irradiation of acoustic neuromas using single treatments (4, 13–16, 23, 25, 26, 30, 36, 37, 39, 41, 44, 47, 50, 51, 58), a staged course of two to five sessions (42, 43, 48, 65–68), or conventionally fractionated radiotherapy with180-cGy fractions (2, 5, 18, 19, 61). To date, there have been no randomized studies comparing single versus hypofractionated or standard fractionated irradiation. In the absence of such an objective direct evaluation, most comparisons have been based solely on published outcome measures.

Results of Existing Radiosurgery Techniques

The first published report of radiosurgery being used to treat acoustic neuromas was by Leksell (34) and appeared in 1971. Since this seminal publication, multiple retrospective studies have documented the high likelihood of tumor control with such treatment (4, 13–16, 23, 25, 26, 30, 36, 37, 39, 41, 44, 47, 50, 51, 58). Overall rates of tumor control have been shown to be 92 to 100% in the first several years after radiosurgery (13, 16, 23, 28, 30, 36, 41, 44, 58, 59, 62) and 98% after 5 to 10 years of follow-up (30).

Since it was demonstrated that growth cessation of acoustic neuroma was durable after radiosurgery, the lessening of treatment-related morbidity has become the focus of most technical improvements. In particular, an evolving consensus in support of a decrease in the single-stage radiosurgical dose for acoustic neuroma from >14 Gy to <14 Gy (46) has nearly eliminated radiation-induced facial nerve injury and has increased the rate of hearing preservation. Contemporary rates of hearing preservation have been reported to be 71 to 73% (13, 46, 58).

Stereotactic Radiotherapy

The intent behind using conventionally fractionated stereotactic radiotherapy to treat acoustic neuroma is to minimize radiation injury to the adjacent cranial nerves beyond what can be achieved with single-fraction radiosurgery. Several preliminary and retrospective studies have reported improved rates of hearing preservation after standard fractionated treatment of acoustic neuroma, from 68 to 100% at 18 to 23 months (2, 19, 60, 61) and 71 to 85% at 2 and 5 years (18, 55). The long-term control rates after radiotherapy are less well established; given the reduced accuracy and conformality that characterizes most technology for stereotactic radiotherapy, other long-term complications also may be an important consideration.

A recent series was reported by Sawamura et al. (55) using more conventional courses of fractionated radiotherapy for the treatment of acoustic neuromas. This study reviewed 101 patients with acoustic neuromas treated with 20 to 25 fractions for a total of 40 to 50 Gy. Useful hearing preservation rate was 71%, with a 91.4% 5-year tumor control rate. In contrast, a series by Andrews et al. (2) reported on 125 patients, of whom 56 were treated with conventional fractionated of 2 Gy delivered over 5 weeks. These patients were compared with the remaining 69 patients who were treated with a 12-Gy radiosurgery treatment. The authors concluded that tumor control rates were more than 97% for both subgroups of patients and that cranial nerve morbidity was low with the exception of functional hearing preservation, which was 2.5-fold higher in the group receiving conventional fractionated treatments.

The Rationale for Staged Irradiation

Tumor control is not a rationale for staging radiosurgery for acoustic neuroma. Existing radiosurgery techniques consistently result in high rates of tumor control. Again, the primary objective for staging radiosurgery is to minimize radiation-related cranial nerve complications. Despite this goal, it is important to note that by combining a lower dose and greater conformality, contemporary techniques for single-stage stereotactic radiosurgery for acoustic neuromas already have reduced the risk of radiation-induced facial nerve injury to less than 2%. The incidence of facial nerve damage being reported here is similar to that reported in other series. From a practical standpoint, it is much more realistic that staged radiosurgical ablation may demonstrate a benefit in terms of hearing preservation.

Our previously published fractionated radiosurgical experience for acoustic neuroma at Stanford used three 7-Gy stages (21 Gy total dose) separated by 12-hour interfraction intervals (48). This small frame-based series resulted in a 77% rate of hearing preservation (Gardner-Robertson Grade 1 and 2) after 2 years of follow-up. Subsequent to our initial study, multiple reports demonstrated that radiosurgery resulted in high rates of tumor control. This observation formed the basis for a widespread lowering of radiosurgical doses for acoustic neuromas with the objective of further improving the likelihood of saving residual hearing (28, 46). As a result of this general trend, we modified our protocol over the course of the present study by decreasing both the single-stage and total radiosurgical dose to 6 Gy and 18 Gy, respectively. Using the linear quadratic equation, this regimen has the biological equivalence of an 11.5- to 12-Gy single-stage treatment. It was our underlying hypothesis that lowering the radiation dose may improve on our previously reported rates of hearing preservation.

Overall Clinical Outcome: Comparison with Other Techniques

The rate of tumor control encountered in the present series demonstrates the effectiveness of a staged approach and compares favorably with all other radiosurgical series, with a 98% tumor control rate. Furthermore, after 3 years of follow-up, 48% of tumors decreased as assessed on follow-up imaging. Ultimately, even longer follow-up will be needed to establish the definitive rate of control with this technique. However, the likelihood of a benign tumor regrowing 3 years after radiosurgical ablation is believed to be very low (31).

In the current series, 74% of patients with pretreatment Gardner-Robertson Grade 1 to 2 hearing maintained preradiosurgery levels of hearing as measured on audiogram (70% hearing unchanged, 4% hearing improved). This result is not statistically different than our previously reported much smaller series using an older protocol and less sophisticated technology. However, the length of follow-up in the present series is significantly longer and may be more representative of the ultimate long-term hearing outcome that can be achieved with staged radiosurgery. Although the absence of permanent facial and trigeminal nerve complications experienced in the current series is superior to the outcome described in our earlier report, the relatively small number of subjects prevents this finding from being statistically significant. Nevertheless, it is plausible that a significantly larger clinical series could demonstrate a benefit from the greater radiosurgical accuracy and conformality that is now possible with the CyberKnife.

Other Hypofractionated Stereotactic Irradiation Trials for Acoustic Neuroma

Over the past 5 years, several other reports also have documented the benefits of using hypofractionated stereotactic irradiation in three to five stages to control acoustic neuromas (43, 48, 55, 57, 65–68). Williams (66) treated 150 acoustic neuroma patients with either 5 treatments of 5 Gy for tumors smaller than 3.0 cm or 10 treatments of 3 Gy for tumors larger than 3.0 cm; approximately 90% of patients were treated using the 5-fraction, 5-Gy regimen. Although follow-up was only 1 year, no tumor increased in size and there was no instance of facial nerve injury. Only two patients in this series reported transient facial sensory changes. After 1 year, Gardner-Robertson Grade 1 or 2 hearing was maintained in 70% of patients when the tumor was smaller than 3.0 cm and was treated with the 5-fraction, 5-Gy regimen. Somewhat surprisingly, Williams reported that the hearing preservation rate was 100% among patients with the larger (>3.0 cm) lesions. Although this was only a preliminary observation, it seems reasonable to speculate that this phenomenon may stem in part from some anatomic or biological peculiarity that is unique to the rare acoustic neuroma that reaches 3 cm without the patient losing all hearing.

Meijer et al. (42) reported on the results of hypofractionated radiosurgery in 80 patients with acoustic neuromas using either 5 treatments of 4 Gy or 5 treatments of 5 Gy. Overall 5-year actuarial tumor control rates and facial nerve preservation were 94 and 96%, respectively. Although normal trigeminal nerve function was retained in 98% of patients, the hearing preservation rate at 5 years was 66% (43). Besides using different dose/fraction regimens, both of these clinical series used radiosurgical techniques that are less conformal and less accurate than that described in the current report. The significance of such technical specifications to patient outcome, if any, is uncertain.

Drawbacks of Staged or Fractionated Treatments

Despite the potential benefits of staged or hypofractionated treatment, there are drawbacks to this approach. Multiple treatment sessions result in added inconvenience and logistical challenges for most patients. Furthermore, multiple treatments obviously will require physicians to invest additional time. Although each individual stage or fraction may be relatively short, total treatment time will always be longer than single-stage radiosurgery, providing neither conformality nor accuracy is sacrificed. Whether such technical nuances measurably impact treatment outcome is a relevant question for which there is, as yet, no definite answer. However, with radiosurgery, conformality and targeting accuracy generally are acknowledged to be important variables in determining the extent of cranial nerve irradiation, which in turn directly impacts the risk of surgical morbidity (35, 45). Only further investigation can establish whether a less critical threshold exists with staged treatment. Regardless, from a theoretical perspective it seems likely that there should be some finite benefit to more precise irradiation with absolutely no downside risk. Until proven otherwise, we believe that it is prudent for staged radiosurgical techniques to maintain approximately the same level of accuracy and conformality achieved by the best of conventional frame-based devices.

Limitations of the Present Study

There are several drawbacks to this current clinical report. Given the long natural history of benign tumors like acoustic neuromas, which are best discussed in terms of decades and not years, the length of follow-up in this series is relatively short. Because some acoustic neuromas can lay dormant for years and even decades, longer follow-up is necessary before we can be certain that such tumors are definitively ablated. A similar criticism exists for nearly all other published series involving the radiosurgery for acoustic neuroma. Moreover, the short-term outcome reported here closely parallels that described in the few radiosurgical studies with long-term follow-up. Although we would expect the results in more recently treated patients at a minimum to mirror our earlier experience using less sophisticated radiosurgical technology, only longer follow-up can confirm such an impression. Additionally, although most cranial nerve dysfunction after radiosurgery occurs in the first few years, it certainly is possible that hearing will worsen in some patients with longer follow-up (45). However, among the vast majority of publications examining the outcome after stereotactic irradiation of acoustic neuromas, treatment-related toxicity primarily occurred during the first 36 months after treatment (18, 31, 33, 44, 48, 49, 60, 61).

Another weakness of the present series concerns the choice of total radiation dose and fraction number. Our decision to use three stages in the radiosurgical treatment of acoustic neuroma largely is serendipitous. The basic concept was first explored at Stanford with a frame-based linear accelerator radiosurgical system for inpatients with neurofibromatosis, which was driven largely by a desire to improve the rate of hearing preservation. For practical reasons, it was believed that a patient could realistically tolerate a frame for only 36 hours, and in this period, it was possible to administer 3 fractions based on an interfraction interval of at least 8 to 10 hours. Our current approach stems largely from this prior experience. It is quite possible, and even probable, that an even more optimal dose/fraction regimen exists for staged acoustic neuroma. Other groups have proposed regimens with anywhere from four to five stages or more for acoustic neuromas (42, 43, 65–68). Still other groups advocate conventional radiotherapy using 1.8- to 2-Gy fractions to a total dose of 54 Gy (2, 5, 18, 19, 61). Even if a well-structured randomized trial were to be organized immediately, it could well be a decade or more before the optimal dose and number of treatments is known, given the prolonged natural history of these tumors. Although it seems unlikely to be of consequence here, one must always consider the possibility that some type of selection bias may have skewed the outcome of any retrospective clinical study.

CONCLUSION

Over a mean of 4 years of follow-up, we have found that staged image-guided radiosurgery for acoustic neuromas results in very high tumor control rates, negligible facial nerve injury, and a possible increased likelihood of hearing preservation compared with other radiosurgical techniques. Additional studies and longer follow-up will be required to confirm this impression and to determine the optimal dose and staging regimen. The ultimate benefits of using staged radiosurgery to ablate acoustic neuroma would seem to be best evaluated in a randomized prospective trial.

DISCLOSURE

JRA is Chief Medical Officer of Accuray, Inc.

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COMMENTS

Chang et al. present results on a series of 61 patients with average 4-year follow-up who had hypofractionated irradiation of their vestibular schwannoma using the CyberKnife. Three fractions were delivered to a total dose of 18 or 21 Gy. The rationale for this dosing regimen is somewhat arbitrary, and, indeed, there has been much inconsistency with fractionation approaches for these tumors. This makes any comparison of results with fractionation complicated.

Nevertheless, the authors found satisfactory rates of tumor growth control with low rates of facial neuropathy and acceptable hearing preservation in early follow-up examinations. Clearly, the hearing preservation rate identified after irradiation exceeded that after surgical resection in almost all series.

More and more patients are choosing stereotactic radiosurgery for small or medium sized acoustic neuromata, and others are offered fractionated irradiation, depending on a centers experience. The Internet is full of unsubstantiated claims that one approach is far superior over another (e.g., open surgery is barbaric or radiation scars everything and can cause cancer), usually written by those with no interest in the peer-review process. Patients are educating themselves, seeking multiple opinions, and reading the literature if they can find it—and most can. Nevertheless, many are confused. The literature on surgical resection is well established, but most of it is fairly outdated. Do surgeons quote their own results or those of others published years ago? The literature on stereotactic radiosurgery, particularly with the gamma knife is established as well, and many reports have recently been published from a number of institutions, including long-term data that extends to 15 years. Reports on fractionated irradiation are more recent, with some data (like this report) extending to a mean of 4 years. Some reports show better results than others, possibly because of patient selection. For example, the report by Sawamura et al. (1) on fractionated irradiation (101 patients who had 40–50 Gy over 20–25 fractions) noted a tumor control rate of 91.4%, hearing preservation of 71%, facial neuropathy of 4%, trigeminal neuropathy of 14%, and hydrocephalus with the need for a shunt in 11%. The median tumor size in their series was 19 mm in diameter with a range of 3 to 40 mm. In my opinion, such complication rates are not comparable to the 'best results of radiosurgery,' as proposed in the conclusion of their abstract.

I do not know if Chang et al. will further modify their dose or fractionation regimen, change to a radiosurgery approach, or simply continue to collect data with their current technique. There is no doubt that the bar has been raised in the management of patients with vestibular schwannomas. I would suggest that there be more consistency in our techniques, so that we may acquire data from different centers more quickly, hopefully leading to tangible improvements and better outcomes.

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1. Sawamura Y, Shirato H, Sakamoto T, Aoyama H, Suzuki K, Onimaru R, Isu T, Fukuda S, Miyasaka K: Management of vestibular schwannoma by fractionated stereotactic radiotherapy and associated cerebrospinal fluid malabsorption. **J Neurosurg** 99:685–692, 2003.

This article represents the first large CyberKnife-based radiosurgery experience for the treatment of acoustic neuromata. The current results support the same institution's previous experience with the use of a fixed frame: notably excellent tumor control and comparable cranial nerve preservation rates, including a hearing preservation rate of greater than 70%. The use of a non-invasive head fixation device with an Aquaplast mask represents an advance over fixed frame treatments for the staged technique.

I share the authors' belief that a fractionation technique will provide the highest rate of hearing preservation, more so than surgery or single fraction radiosurgery. Single fraction radiosurgery at a 12 Gy and 50% isodose prescription represents the optimal dose iteration for this technique with reports of hearing preservation rates achievable at somewhere between 50 and 70%. With dose iterations, the fractionated technique holds the promise of higher hearing preservation rates. The ideal dose per fraction and total dose delivered should yield a high rate of tumor control and comparably high serviceable hearing preservation rate. This ideal regimen as yet remains unknown, as the authors point out, and, as in the current study, investigators are iterating the dose fractions and total doses downward to achieve higher hearing preservation rates. Although dropping the dose from 21 to 18 Gy yielded the same hearing preservation rate, the tumor control rate was comparable, thus justifying future dose reductions as the authors explore this technique to see if hearing preservation rates improve while maintaining high tumor control rates. Two years ago, we decreased our daily dose from 2 Gy to 1.8 Gy and our total dose from 50.4 Gy to 46.8 Gy to increase hearing preservation. We have just begun to examine the results.

An additional issue not discussed in this article is dose homogeneity. We have installed the Novalis M3 collimation system (BrainLAB, Heimstetten, Germany), which achieves high conformality and simultaneously high dose homogeneity with dynamic arc shaping. We share the beliefs of the group at the Charite Hospital in Berlin that single isocenter dose prescriptions provide both high dose conformality and homogeneity, and thus contribute to higher hearing preservation rates for patients with acoustic tumors.

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Stanford is one of the groups testing stereotactic hypofractionated irradiation for acoustic tumors. The CyberKnife confers the mobility to allow fractionated stereotactic treatments without multiple applications of a stereotactic frame. Presumably, this is the reason that this particular group has gone in that direction.

Frameless treatment is becoming a revolution in brain and spine radiotherapy and radiosurgery. The new technology of cone-beam computed tomography, which is soon to be available on most linear accelerators in radiation oncology facilities, will rival the CyberKnife by allowing digital tomographic images to be acquired to confirm and automatically adjust patient position as the radiation treatment progresses (1). In addition to being frameless, such a conventional linear accelerator-based system has the advantage of the use of 3-mm multileaf collimators for superior conformality and precision through conformal and even intensity-modulated treatments of the central nervous system.

The principal rationale for fractionating the radiation treatment of acoustic tumors is improved hearing preservation. As reported here, fractionated treatment using the CyberKnife has not improved these results at Stanford over their previous results with frame-based single fraction treatments. This is not surprising, because in a single-institution study from Amsterdam, single-fraction radiosurgery seemed to be as good as fractionated stereotactic radiation therapy with respect to local control, facial nerve preservation, and hearing preservation (2). Use of intensity modulated radiotherapy in single-fraction radiosurgery can decrease the maximum dose to the acoustic nerve by approximately 20% from the prescription dose and is being explored at our institution.

Because acoustic neuromata are such slow-growing tumors, it will be a long time until we understand the control rates that are being achieved with various doses and fractionation schemes. To try to further fractionate or further reduce dosage to improve hearing conservation will at some point adversely affect control rates, and we will not understand all of this for a long while. Because we already have excellent results with this tumor with single fraction treatments, it is difficult to be enthusiastic about such 'tinkering.'

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1. Jaffray KD, Siewerdsen JH, Wong JW, Martinez AA: Flat-panel cone-beam computed tomography for image-guided radiation therapy. **Int J Radiat Oncology Biol Phys** 53:1337–1349, 2002.
2. Meijer OW, Vandertop WP, Baayen JC, Slotman BJ: Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: A single-institution study. **Int J Radiat Oncol Biol Phys** 56:1390–1396, 2003.

The standard non-surgical treatment regimen for patients with acoustic neuromata has been radiosurgery. When early results indicated modestly high cranial nerve injury rates, two simultaneous efforts were initiated in the modification of radiation delivery. One was to reduce doses and improve conformality with radiosurgery, whereas another was to develop delivery systems for fractionated stereotactic radiotherapy. Both efforts have clearly reduced cranial nerve injury, and damage to the 7th and 8th nerves in particular. Most patients who have undergone stereotactic radiotherapy have been treated with relatively conservative fractionation schedules with 54 Gy delivered in 30 fractions. However, other groups have used hypofractionated schemes of four, five, or ten fractions usually of 5, 4, or 3 Gy per fraction, respectively. The authors of this report of used three fractions of 6 to 7 Gy for total doses of 18 to 21 Gy delivered over a 24-hour period. This fractionation scheme is certainly more convenient for the patient compared with more routine fractionation schedules used at other institutions. Tumor control, hearing, and 5th and 7th nerve preservation all seem quite excellent with an average observation period of 4 years. The rationale for this treatment schedule is based on experimental and clinical experience using hyperfractionated radiotherapy that show that a minimum of 6 hours between fractions is required for substantial (though not complete) central nervous system repair. Although these results seem excellent, I still have concerns about the treatment schedule. When treating such a benign tumor with radiation, what is the rush?

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*Scanning electron micrographs showing embryoid bodies in clusters of undifferentiated cells. Immunoreactivity (*green*) indicates that the cells possess immunomarkers for neural precursors; nuclei are counterstained (*blue*). (*From, *Liu S, Qu Y, Stewart TJ, Howard MJ, Chakrabortty S, Holekamp TF, McDonald JW: Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation.* ***Proc Natl Acad Sci U S A*** *97:6126–6131, 2000.*)