Radiosurgery for Acoustic Neurinomas (Vestibular Schwannomas)

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Key words: radiosurgery, acoustic neurinoma, vestibular schwannoma, stereotactic radiation, radiation dose

Abstract

Background: Radiosurgery is a therapeutic technique characterized by the delivery of a single high dose of ionizing radiation from an external source to a precisely defined intracranial target. The application of radiosurgery to the treatment of acoustic neurinomas has increased substantially in the last decade. Most of the published experience pertains to the use of the gamma knife.

Objectives: To report the experience at the first Israeli Linear Accelerator Radiosurgery Unit in the management of 44 patients with acoustic neurinomas.

Methods: We analyzed the clinical records and imaging studies of all patients undergoing radiosurgery for acoustic neurinomas between 1993 and 1997, and quanitified the changes in tumor volume, hearing status, and facial and trigeminal nerve function. The contribution of radiation dose and original tumor volume upon those variables was also studied.

Results: At a mean follow-up of 32 months (range 12–60), 98% of the tumors were controlled (75% had shrunk; 23% had stable volume). The actuarial hearing preservation rate was 71%. New transient facial neuropathy developed in 24% of the patients, persisting in mild degrees in 8%. Neuropathy correlated primarily with tumor volume. Tumors with volumes >4 ml were at high risk when marginal radiation doses were >1,400 cGy. Dose reduction to a maximum of 1,400 cGy produced no neuropathies in the last 20 patients, still preserving tumor control rates.

Conclusions: Radiosurgery is an effective and cost-efficient therapeutic modality for newly diagnosed acoustic neurinomas in the elderly or medically infirm population, and for all residual or recurrent tumors after conventional surgery.

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Vestibular schwannomas (also known as acoustic neurinomas) are the most frequent lesions arising in the cerebellopontine angle. They are benign and slow-growing tumors, with a mean delay of 4 years from the presenting symptom to diagnosis [1]. Their annual incidence has been estimated to be 1:100,000 [2], or 8% of all intracranial tumors. Ninety-five percent of acoustic neurinomas present unilaterally. Bilateral tumors (5%) are pathognomonic of neurofibromatosis Type 2 [3]. Although the term acoustic neurinoma is commonly used, the tumor is histologically a schwannoma and characteristically arises from the vestibular nerve. The most common presenting symptom is unilateral sensorineural hearing loss, with more than 95% of patients experiencing some hearing loss in the course of their illness. Other symptoms include tinnitus (70%), vertigo (20%), and trigeminal (14–28%) and facial nerve dysfunction (10%). Late symptoms include hydrocephalus, visual loss, diplopia, and long tract signs [1]. With the advent of magnetic resonance imaging, there has been an increase in the diagnosis of small and medium-sized tumors [4].

Surgery has been the traditional treatment for vestibular schwannomas. Results have improved steadily since the introduction of the operative microscope and earlier diagnosis obtainable with new imaging techniques. Complete resection of a vestibular schwannoma with anatomic preservation of the facial nerve constitutes standard therapy, with mortality rates of ~1% [5,6]. However, in patients with bilateral tumors, in those whose tumors are in the only hearing ear, and in elderly or medically infirm patients, anesthesia and surgery may pose an unacceptable high risk [7]. The same applies where microsurgical expertise in removal of these tumors is less than standard. These considerations have justified the development of alternative treatments.

Lars Leksell introduced the concept of stereotactic radiosurgery in 1951 [8]. The term is now applied to any technique that delivers a high *single* dose of ionizing radiation from an external source to a stereotactically defined intracranial target, achieving a steep radiation fall-off beyond the limits of the lesion [9]. Several radiation sources have been adapted to the delivery of radiosurgery. For practical reasons, photon beam radiosurgery has become the most widespread modality. The first photon beam system, the gamma knife, was introduced in 1968 by Leksell and coworkers [9]. In the early and mid-1980s several groups began adapting linear accelerators as the radiation source for radiosurgery [10–12] [Figure 1].

With the introduction of LINAC[1] radiosurgery, there has been a steep increase in the number of centers throughout the world; yet despite their ubiquity, the number of communications reporting results of LINAC radiosurgery for acoustic neurinomas is sparse [13]. In this paper, we review our experience with LINAC radiosurgery of vestibular schwannomas.

Patients and Tumor Characteristics

From February 1993 through December 1997, 48 patients diagnosed with vestibular schwannomas underwent LINAC radiosurgery at the Sheba Medical Center. They represented 14% of our unit's patient load. Three patients were lost to follow-up. Of the remaining 45, 44 completed between 12 and 60 months follow-up (mean 32) at the

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[1] LINAC = linear accelerator

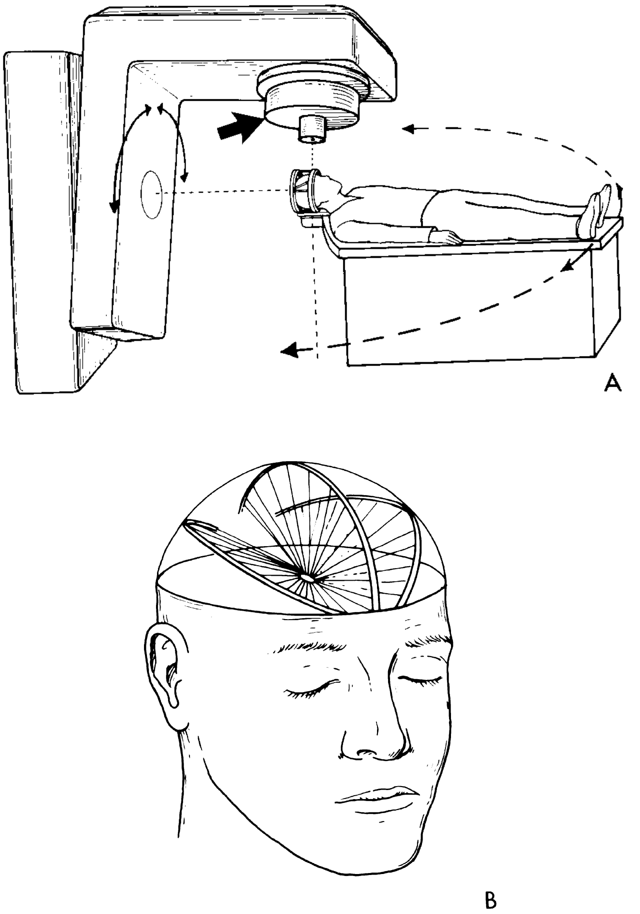

Figure 1. [A] Diagram of a linear accelerator. The high-energy photons are electronically generated in the accelerator. The photon beam exits through the gantry (arrowhead). For conventional radiosurgery, the photon beam cross-diameter is reduced to a pencil shape by circular collimators of different apertures. The patient rests on the couch, the stereotactic frame applied to his head. The target within the head is brought to coincide with the accelerator's "isocenter" which is determined by the intersection of three axes: the axis of rotation of the patient's couch, the axis of rotation of the accelerator, and the axis of the radiation beam. [B] In radiosurgery the accelerator rotates around the patient's head, describing a segment of arc centered on the target lesion. Once an arc is completed, the patient's couch is rotated a few degrees so that a different area of the head is exposed to the radiation beam. Several radiation arcs are delivered, each composed of hundreds of radiation beams intersecting at the target.

time of this writing and configure the database for this report. All the patients, 18 males and 26 females with a mean age of 57 years (range 29–78), had unilateral tumors. Tumors considered for radiosurgery had a maximum mediolateral diameter of 30 mm. Patients with larger tumors were offered conventional microsurgery. Surgery aimed at reducing the tumor volume to a size considered compatible with radiosurgery was undertaken in three patients in this series after initial referral. In those cases, radiosurgery was administered 6–12 months after suboccipital craniotomy. The delay between treatments was necessary to allow for resolution of early postoperative changes. Seven other patients who had undergone previous attempts at surgical removal (between 1 and 3) were referred due to residual or recurrent tumor. Tumor volumes ranged from 1 to 11 ml (mean 3.75). Maximal mediolateral tumor diameter ranged from 10 to 31 mm (mean 20).

Assessment

Patients were assessed, before and after treatment, by clinical examination, gadolinium-enhanced MRI, and audiogram. Volume was determined by measuring the maximum tumor diameter under magnification in each orthogonal view in contrast-enhanced MRI. Hearing on the affected side was defined as serviceable when the speech discrimination score was $\geq$70%. Thirteen patients had useful hearing before treatment. Facial nerve function was assessed according to the classification of Brackman and House [14] [Table 1]. Ten patients had facial neuropathy before radiosurgery: 2 of them had no previous surgery (one patient with grade 2 paresis and one with grade 6), and 8 had neuropathy following previous attempts (1 to 3) at surgical removal (six B&H^2 6, one B&H 4, and one B&H 5). Trigeminal nerve function was assessed by examination of touch and pinprick sensation in the areas of the three nerve divisions. Sensation was given a score of 0–100% as compared to the unaffected side, and registered graphically on the patient's chart. Seven patients had sensory deficit before radiosurgery (five following surgery).

Follow-up

Initially patients were followed at 6-month intervals, but in the last 2 years the policy was changed to yearly follow-up. The mean follow-up for this series was 32 months (range 12–60).

Radiosurgical technique

Patients were hospitalized for 24 hours. On admission, a stereotactic head ring was applied bedside to the patient's head under local anesthesia. Contrast-enhanced computerized tomography was performed with a stereotactic localizer. The whole head was scanned with 1–2 mm contiguous slices. The images were transferred by tape to a Sun Sparc2 computer workstation (Sun Microsystems, Mountain View, CA, USA) and processed with software developed at the University of Florida, USA. Forty-five cases were irradiated with a single isocenter (5–9 non-coplanar arcs). Different combinations of arc span, arc weighting, angle of arc incidence, and number of arcs were used to achieve maximum conformity of the treatment dose to the borders of the tumor, as well as the steepest radiation fall-off towards the nearby critical structures [Figure 2]. Five tumors with irregular shapes were treated with two (four cases) or three (one case) isocenters. The mean radiation dose specified to the tumor margin was 1,455 cGy (range 1,100–2,000). During the first 2 years of activity the dose range varied between 1,500 and 2,000 cGy, after which the prescribed dose was reduced to 1,100–1,400 cGy, varying with tumor volume. Every attempt was made to achieve homogeneity in dose distribution across the tumor by specifying the treatment dose to the highest possible isodose area (68–90%, mean 79%).

A Varian 600 C linear accelerator (Varian Medical Instruments, Palo Alto, CA, USA) was modified with removable precision parts for radiosurgery delivery. A stereotactic positioning device was placed at the machine isocenter before treatment, and a metallic holder for small-aperture collimators was affixed to the radiation gantry.

Table 1. Clinical assessment of the facial nerve function [14]

Grade 1 – Normal facial function in all areas	
Grade 2 – Mild dysfunction	a. Gross: slight weakness noticeable on close inspection, possibility of very slight synkinesis b. At rest: normal symmetry and tone c. Motion: Forehead – slight to moderate movement Eye – complete closure with effort Mouth – slight asymmetry
Grade 3 – Moderate dysfunction	a. Gross: obvious but not disfiguring difference between two sides: b. Noticeable but not severe synkinesis c. Motion: Forehead – slight to moderate movement Eye – complete closure with effort Mouth – slightly weak with maximal effort
Grade 4 – Moderate to severe dysfunction	a. Gross: obvious weakness and/or disfiguring asymmetry b. Motion: Forehead – none Eye – incomplete closure Mouth – asymmetric with maximal effort
Grade 5 – Severe dysfunction	a. Gross: barely perceptible motion only b. At rest: asymmetry c. Motion: Forehead – none Eye – incomplete closure
Grade 6 – Total paralysis; no movement	

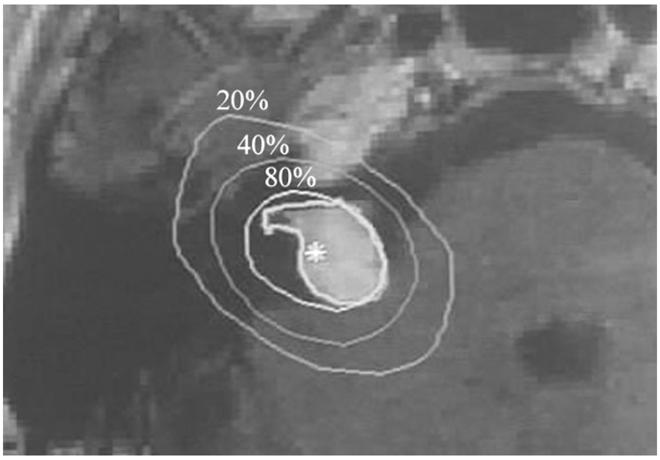

Figure 2. Detail of a stereotactic axial MRI image showing a typical acoustic neurinoma during computerized treatment planning, using a single-isocenter (single shot) radiosurgery plan. By combining different radiation arc spans, angles of arc incidence, and different collimator sizes, a radiation shape tightly conforming to the tumor can be generated. The treatment dose (defined by the 80% circle) closely follows the boundaries of the tumor in the anterior, medial and superior (not shown) aspects of the tumor, where the facial nerve, brainstem, and trigeminal nerve respectively course. The posterior–inferior areas of the tumor are occupied by the lateral cerebellum and the inferior cranial nerves, which are resistant to radiation damage. Note the steep radiation fall-off beyond the tumor margin (the 40% circle) represents 50% of the treatment dose, and the outer circle 20% of the treatment dose. The distance between the 50% and the 20% isodose lines is 4 mm).

The system's mechanical precision was verified before each treatment by irradiation of dummy targets from different gantry and patient's couch positions. The maximal isocenter deviation was 0.5 mm in all cases. The patient was then brought into the LINAC suite and placed supine on the couch, and the stereotactic ring around his or her head was firmly attached to the isocentric positioner. Radiation was delivered through multiple non-coplanar radiation arcs. Treatment time varied from 20 to 45 min. The stereotactic ring was removed from the patient's head immediately after radiation. Patients were discharged on the morning following treatment and allowed to return immediately to their normal activities. No specific medication was prescribed aside from non-narcotic analgesics.

Results

Acute side effects

One patient with a recurrent tumor developed facial neuropathy 3 days after treatment. A few other patients complained of headaches lasting for 2–3 days. No other acute side effects were noted.

Tumor changes

Early imaging changes

In patients assessed 3 and 6 months after radiosurgery, two different early imaging changes were seen:

- Loss of tumor's central contrast enhancement. This change was frequently observed and was usually transient, with several tumors recovering homogeneous contrast enhancement at later follow-up. Loss of central contrast enhancement had no correlation with the occurrence of untoward volumetric changes.
- Early tumor enlargement. This phenomenon was observed in 11 patients during the first year of follow-up and was associated with loss of contrast-enhancement in each case. Eight patients developed concomitant facial neuropathy. Volume reduction occurred later in all of these tumors, as compared to their original size at the time of radiosurgery.

Late volume changes

Thirty-three tumors (75%) reduced their volume by 15–90% [Figure 3]. The peak incidence of tumor shrinkage was observed between 24 and 36 months after radiosurgery (80 and 84% respectively). Ten tumors (23%) had preserved their original volumes at the end of follow-up. One patient with a tumor that had originally shrunk proceeded to show a 15% asymptomatic volume enlargement 48 months after treatment. She did not undergo surgery and is stable at the time of this writing (60 months post-radiosurgery). The actuarial tumor control rate was 98%.

Hearing

Thirteen patients had preserved hearing before treatment, 9 of who retained serviceable hearing at the end of follow-up. Another patient had a 50% speech discrimination rate before radiosurgery that improved to a score of 80%. The hearing preservation rate was therefore 71%.

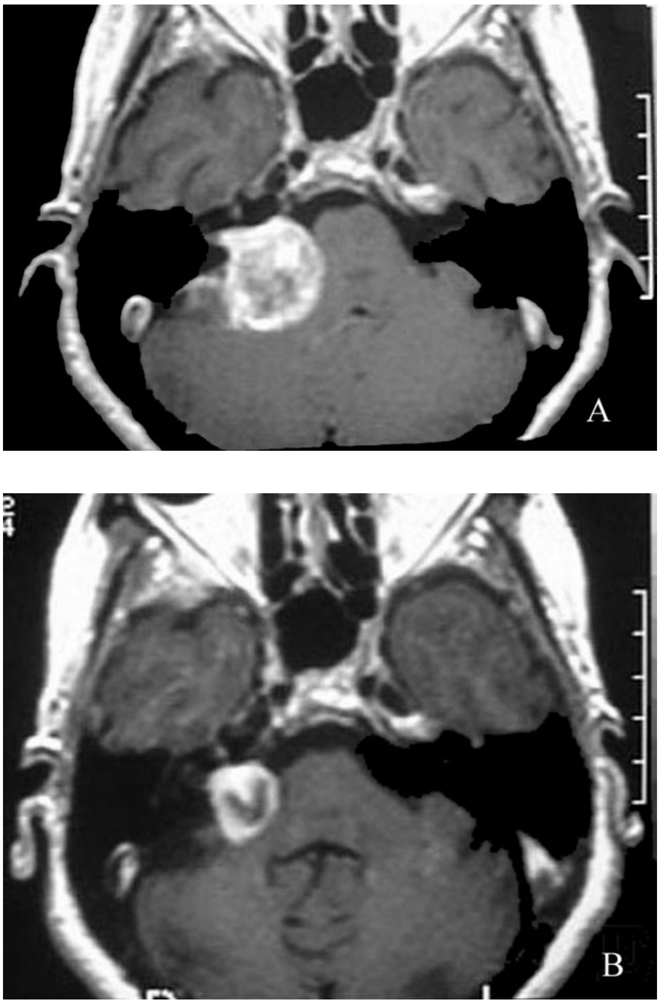

Figure 3. Axial MRI slices of an acoustic tumor [A] before, and [B] 2 years after radiosurgery. The patient had a 50% speech discrimination rate on the affected side before treatment, which rose to 80% at the time of the follow-up study.

Facial nerve

New facial neuropathy developed in 9 of 37 patients (24%) who had normal or partial facial nerve function before radiosurgery. In all cases the facial neuropathy developed within 1 year of radiosurgery, but improved or resolved over time in all of them. At the time of this writing, three patients have some remaining weakness (1 grade 4, 1 grade 3, 1 grade 2). This makes for an actuarial facial neuropathy rate of 8%. Two patients with preoperative facial nerve dysfunction showed improvement in their facial nerve function after treatment.

The occurrence of neuropathy in this series correlated closely with radiation dose and tumor volume. Facial neuropathy developed in 1/18 patients (5.5%) receiving up to 1,400 cGy, and in 8/19 (42%) receiving 1,500–2,000 cGy. In 21 tumors with volumes between 0.8 and 3.7 ml there were 2 neuropathies (9.5%), as compared to 7 neuropathies in 13 tumors (54%) with volumes of 4–11 ml. Since the radiation dose in these series was not preselected according to tumor size, but rather changed for all tumors at a given time point, the relative contribution of radiation dose and tumor volume on the incidence of neuropathy could be assessed without bias. As seen in Figure 4, tumor volume was the most significant risk factor, with incidence peaking for radiation doses above 1,400 cGy.

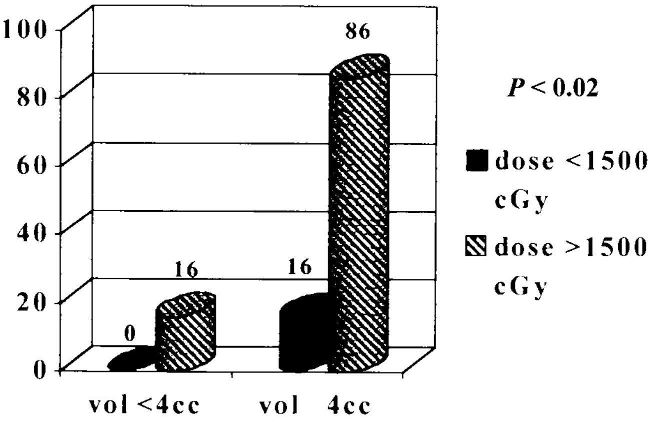

Figure 4. Incidence of facial neuropathy, as function of dose and volume. The significant contribution of volume to the appearance of neuropathy becomes evident by the high complication rate observed in large tumors irradiated with doses > 1,500 cGy. (Fisher's exact probability test, $P < 0.02$.).

Trigeminal nerve

New trigeminal neuropathy developed in 18% of patients, together with facial neuropathy in each case. One patient developed deafferentation pain in the hypoesthetic facial area.

Other complications

No patient developed hydrocephalus, vagal or glossopharyngeal nerve dysfunction, cerebellar or long tract signs.

Discussion

Surgery or radiosurgery?

Acoustic neurinomas have been the subject of surgical removal since the early days of modern neurosurgery. Refinements in technique have not only produced increased rates of facial nerve preservation but have also increased the chances for hearing preservation. Nonetheless, a recent survey of 1,579 patients who underwent resection of acoustic neurinomas between 1989 and 1994 [15] found a 44% rate of facial weakness, 11% rate of postoperative cerebrospinal fluid leakage, and 9% rate of persistent balance disturbance after one year. Recurrence of persistent tumor was found in 7.8% of patients.

M. Samii, the neurosurgeon with the most extensive experience in acoustic neurinoma surgery, recently reported the results of 1,000 cases operated through the suboccipital approach. Total removal was achieved in 979 tumors. The recurrence rate was 0.7%. Complications included a mortality rate of 1.1%, acute facial paresis in 45%, and other major neurological complications in ~6% [5]. Hearing preservation was 39.5% [16]. In Israel, the group from Hadassah reported on 85 patients who underwent microsurgical removal of acoustic neurinomas between 1994 and 1998 [17]. Radical resection was achieved in 76.5%. Immediate postoperative facial neuropathy of varying degrees was observed in 79%. On late follow-up 37.6% had persistent paresis. Functional hearing was preserved in 16.5%. Other complications included cerebrospinal fluid leak (22.4%), infection (11.8%), cerebellar bleeding (7.1%), and hydrocephalus (3.5%).

Gamma knife radiosurgery for these tumors was initiated in Sweden in 1968. In 1988 Norén et al. [18] reviewed their results for the first 180 patients and reported a facial neuropathy rate of 15% following doses of 1,800–2,500 cGy to the periphery of the tumor. When radiosurgery was initiated in the United States in the second half of the 1980s using the same doses, it soon became clear that the incidence of facial neuropathy was much higher. Flickinger et al. [19] reported facial neuropathy in 33% and trigeminal neuropathy in 37%, all of which improved over time. Mendenhall et al. [13] had similar results with LINAC radiosurgery. A gradual reduction in the prescribed radiation dose to these tumors was initiated at the end of the 1980s to reduce neuropathic complications. No data were available to define how much to reduce the radiation dose and, no less important, how this dose reduction would affect the tumor growth control rate.

The mean dose initially used in our series of acoustic neurinomas (1,586 cGy) was part of this trend and was empirically determined. Subsequent experience showed that neuropathies still had a relatively high rate (close to 30% transient facial and/or trigeminal nerve complications). Although this acute neuropathy rate was already lower than that reported for "best microsurgical series" (>40% acute facial neuropathy in Sammii's series), it was still considered excessive for a noninvasive therapy. In 1995 we further reduced the therapeutic radiation dose for acoustic neurinomas to 1,100–1,400 cGy, varying according to tumor size (in particular, the mediolateral extent of the tumor). This dose range virtually eliminated the incidence of neuropathies in the last 20 tumors irradiated in this series. A similar experience has recently been reported by other centers, with hearing preservation rates exceeding 60% [20]. Tumor-control rates have remained at previous levels in spite of the reduced radiation doses [13], including series with follow-ups approaching 10 years [20,21].

It is frequently argued that radiosurgery does not actually cure acoustic neurinomas, since the tumor shadow remains in imaging techniques years after treatment; and that surgery, by physically removing the tumor from the skull, would achieve a more definitive outcome. To be sure, complete surgical resection of a benign tumor offers a straightforward measure of outcome — the tumor is no longer there. Nonetheless, even the absence of a tumor shadow is no proof of cure, as attested by recurrence rates of 1–10% after seemingly complete removals.

Radiosurgery of a benign tumor does not result in, nor does it pursue its physical elimination. The goal of radiosurgery is the *biological* elimination of the tumor. Since radiosurgery deals with tumors that — if unchanged in their volume — will not jeopardize the patient's life or neurological function, the physical persistence of the tumor shadow is irrelevant to outcome.

The reported recurrence rate of acoustic neurinoma following surgery varies between 1 and 8% for totally resected tumors and 16% for subtotally resected tumors [22]. Most recurrences become apparent during the first 4 years after surgery. Consequently, in the absence of findings in imaging studies 5–6 years after surgery, follow-up is usually discontinued. Since there is no current imaging modality capable of assessing biological viability, verification of tumor control after radiosurgery requires a more extended follow-up.

The indications for radiosurgery in acoustic neurinomas have changed in the past few years, paralleling the experience gained with the technique. During our first few years of activity, we recommended radiosurgery for acoustic tumors in the elderly, for tumors in the only hearing side, for patients with medical infirmity posing a significant surgical risk, and for recurrent tumors. Currently, and based upon the comparative results presented herein for tumor control, facial nerve function and hearing preservation, we believe that radiosurgery should be offered as the primary treatment modality for acoustic neurinomas of suitable size, regardless of the patient's medical status.

Linear accelerator or gamma knife radiosurgery

The gamma knife became available in Sweden in 1968. Since 1987, with the establishment of the first gamma knife unit in the United States, radiosurgery rapidly expanded, becoming a mainstream therapeutic modality. The inception of LINAC radiosurgery in the 1980s generated a protracted controversy as to the optimal radiosurgical instrument. This controversy is now obsolete, since the growing body of information confirms (as would be expected) that the results of treatment for all pathologies are similar with both techniques, when comparing experienced and quality-driven groups.

The major assets of the gamma knife are its intrinsic mechanical accuracy and ease of use. Its major drawbacks are the limited diameter of the radiation beam and its fixed basic geometry. For technical reasons, the largest beam cross-section available with the gamma knife is 18 mm. When the lesion has a larger diameter, treatment with the gamma knife requires the use of multiple isocenters (multiple shots) to cover the target, regardless of its geometry. The use of multiple isocenters results in an increased radiation dose that is absorbed *outside* of the treatment volume. When the target is close to critical structures, or when the target is relatively large, this increased radiation can be potentially damaging to the normal brain.

The energy of the photon beams delivered by the gamma knife or a standard 6 meV LINAC is in the same range. In contrast to the gamma knife, there is no physical limitation to the beam cross-section that can be produced by a LINAC. Openings of any size between 5 and 50 mm can be shaped by appropriate metallic insets so that, for near spherical targets, LINAC radiosurgery can be administered with a single isocenter. Another intrinsic advantage of LINAC radiosurgery is that the shape of the radiation field can be modified by various combinations of beam size, patient's couch rotation, and radiation source excursion. The versatility of LINAC systems has recently been enhanced by the introduction of the micro-multileaf collimator. This computer-driven device dynamically modifies the cross-sectional shape of the radiation beam so that it accurately matches the shape of the target at any view angle. With this device, any target, even the most irregular one, can be irradiated with a single shot. The main disadvantage attributed to LINAC systems is their potentially reduced mechanical accuracy, since both the radiation source and the patient's couch continuously move during radiation delivery. This disadvantage can easily be overcome by the addition of mechanical gadgets and by continuous verification of the system isocentricity. The system in use at the Sheba Medical Center has a maximal isocenter deviation of 0.5 mm, which is roughly similar to the best-published gamma knife accuracy (0.3 mm)

It has been our policy to treat acoustic neurinomas with as few isocenters as possible, and to comprehend the tumor within a high isodose area (mean 79%) in order to preserve a steep radiation fall-off outside the target. In only five very irregular tumors did we have to resort to two isocenters (four cases), or three isocenters (one case). As described previously, we took great care to conform the treatment dose to the boundary of the tumor in its anterior, superior, and medial aspects (towards the facial nerve, trigeminal nerve, and brainstem respectively). Our findings confirm that single isocenter LINAC-based radiosurgery treatment of acoustic neurinomas achieves results comparable to those obtained with conformation by multiple isocenters and the gamma knife.

Conclusions

A noninvasive treatment technique like radiosurgery has intrinsic appeal in that it does not require actual hospitalization, general anesthesia, post-treatment intensive care, head shaving, skin incision, or craniotomy, and the patient returns immediately after to his or her normal activities. Radiosurgery significantly decreases the social and financial impact that these tumors inflict upon the patient, the family and the community.

The number of patients submitted for initial radiosurgical management of acoustic tumors is increasing. In an era of growing cost-efficiency concerns in health-related management, the role of radiosurgery in acoustic neurinomas is bound to grow. Currently, the administration of radiosurgery as a primary treatment tool in newly diagnosed patients appears justified in the older population. In the young patient, however, concern still remains regarding the theoretical long-term complications of radiation upon a benign tumor. Radiosurgery for acoustic neurinomas has been in use for 30 years, with several thousand patients in follow-up. To date, there is only one report suggesting the possible malignant transformation of an acoustic neurinoma following radiosurgery [23]. Compared to secondary radiation-induced malignancies reported after conventional radiation, malignancies following radiosurgery appear to be an extremely rare event. Nonetheless, until additional long-term data are accumulated, this possibility should be considered when counseling a young patient. Faced with the decision of microsugery versus radiosurgery, the neurosurgeon should take into account the quality of microsurgical techniques available. A neurosurgeon with extensive experience and good results with vestibular schwannoma surgery should primarily offer microsurgical removal to young patients.

Tumors compressing the brainstem and tumors with an intracisternal diameter > 3 cm are, in our opinion, contraindicated for radiosurgical treatment. In these cases, when microsurgery is refused or contraindicated for medical reasons, the option of fractionated stereotactic radiation should be considered. However, no treatment may be the best choice for intracanalicular tumors in elderly patients, particular those with preserved hearing on the affected side.

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