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LINAC Radiosurgery and Radiotherapy Treatment of Acoustic Neuromas

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Acoustic neuromas (ANs) are benign, slow-growing tumors that arise from the Schwann cells of the vestibulocochlear nerve. Although these tumors are benign, their expansion in the internal auditory canal and cerebellopontine angle compresses the cranial nerves and the brainstem [1]. Once diagnosed, the tumors are commonly resected microsurgically, managed conservatively with radiologic surveillance, or treated with radiation therapy [2]. This article focuses on the effectiveness of linear accelerator (LINAC) stereotactic radiosurgery and radiotherapy in AN treatment.

Radiation biology

Radiation-induced damage to the cell machinery has been used to control the proliferation of tumors. Interruption of cell division is a desired effect in cells that have lost the ability to respond to appropriate internal and external surveillance because of mutation. The therapeutic role of ionizing X-rays and gamma rays lies in their ability to compromise the integrity of DNA and other important biologic molecules of the target cell. Specifically, excitation of electrons in molecules exposed to radiation produces reactive, free radicals, which in turn degrade structures that are important for cell survival. Double strand breaks in the DNA are most detrimental to the cell. Effective mechanisms for fixing the double strand breaks, which include nonhomologous end joining and a more precise homologous recombination, are often inadequate to deal with the overwhelming damage to the genetic material, especially in highly mutated tumor cells. These lesions prevent the cell from completing the replication cycle and arrest the growth of the tumor. Excessive radiation damage to DNA and the arrest of mitosis lead to induction of the apoptotic—or programmed—cell death pathway. Radiation damage to phospholipids in the membrane of the cell also acts to trigger cascades that lead to cell death [3,4].

There are two types of ionizing radiation: electromagnetic, which consists of photons or packets of energy, and particulate radiation. The common feature of these forms of radiation is ionization, a process that ejects an excited electron from the target atom. This process occurs when a photon or particle transfers its energy to the target tissue. X-rays and gamma rays are

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indirectly ionizing, whereas charged particles are directly ionizing. X-rays and gamma rays are types of electromagnetic radiation and differ in that an X-ray is a result of a collision between an electron and a target, whereas gamma rays are produced when the contents of the nucleus of an atom return to their initial energy state from an excited level, a process known as gamma decay. As these electromagnetic waves pass through tissue, they are absorbed and produce fast recoil electrons. As this occurs, they lose intensity.

Protons are heavy charged particles that cause damage directly. They have an opposite charge from electrons and have considerably more mass. When a proton beam strikes a target, it deposits almost all of its energy at the end of its range. This characteristic, known as the Bragg peak, can be exploited to deliver high doses to tumors with almost no fall-off of radiation. Helium ions act similarly. Neutrons have no charge and are equivalent to a proton in mass. They are not affected by an electric field. They are also indirectly ionizing, and after interacting with matter they produce recoil protons and alpha particles. Although all other radiation modalities work best on parts of tumors in which oxygen is available, neutron radiation provides an opportunity to target the center of large tumors that are oxygen deficient and types of tumors known to be poorly aerated [5].

Radiosurgery (RS) is a term used for the delivery of ionizing radiation to an intracranial target with the use of stereotactic technique. The exposure of normal, healthy tissues to radiation should be limited, yet significant doses must be delivered to the tumor to have a therapeutic effect. Stereotactic technique facilitates the accomplishment of these goals through accurate localization and targeting of the lesion. The target volume is represented in a three-dimensional space with the use of markers on a fixed frame, the location of which is electronically linked with either CT or MRI scans. Fig. 1 shows the planning of a treatment based on the MRI of a patient with AN. Special care must be taken to isolate and protect the brainstem, which is in close proximity to the target volume. The three-dimensional target created is irradiated from several angles; beams all meet and deliver a high cumulative dose of radiation to a single isocenter. For irregularly shaped targets, more than one isocenter can be used. Three modalities are used to deliver radiation in stereotactic RS [6].

As of 2003, approximately 200,000 patients were treated with gamma knife technology. Gamma knife contains 201 cobalt 60 sources

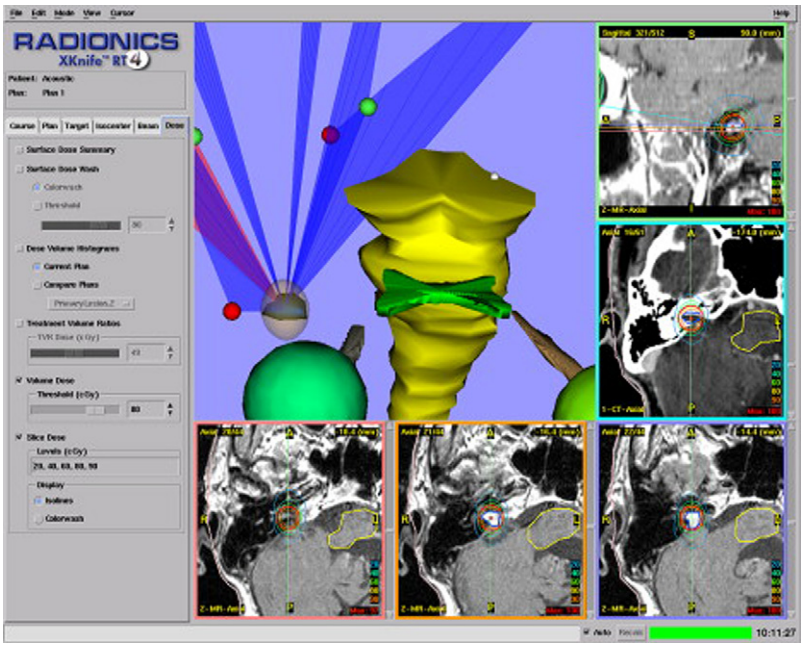

Fig. 1. This computerized treatment plan reveals MRI defining the target (encircled in red) and the area of concern to be isolated, the brainstem encircled by an oblong shape. The mock treatment plan shows the eyes and the brainstem, which are isolated from the target. The radiation beams are shown converging on the target, in this case an intracanalicular AN.

that are collimated using a helmet fitted for patients. Once the treatment is planned using the three-dimensional representation of the target, a patient's head is fixed and the beams from the sources align on multiple isocenters [6].

LINAC is a tool that has long been used to generate X-rays. LINAC uses electromagnetic waves of microwave frequency to accelerate electrons. This first became possible with technology borrowed from high-energy microwave generators used in military radars during World War II. LINAC was first used for radiotherapy in 1953 [7]. More recently, in the early 1980s, it was adapted for use in stereotactic RS. Many LINAC units have been modified for RS, whereas others are designed specifically for this use. It is estimated that more than 30,000 people have undergone LINAC-based RS. LINAC delivers a photon beam of high-energy X-rays through a series of arcs or fixed static fields. Conformality is maximized with the use of micro-multileaf collimators. Conformality can be enhanced further with the use of intensity modulated RS, which varies the intensity of dose within a field to treat tumor and spare normal tissue.

Another modality that has been used in RS over the past 40 years is particle beam irradiation. Two to six beams of charged particles are focused on the target. One example is the use of protons in radiation of intracranial tumors. As in the other two modalities used for RS, the radiation dose that reaches structures outside the target volume is minimized by the effect of the Bragg peak [6].

Stereotactic radiotherapy, or fractionated stereotactic radiotherapy (FSRT), is an alternative to RS. It differs in that the full radiation dose is not administered at one time but is instead divided into several doses. The accuracy of irradiation is reproduced with the use of a head frame, such as the GTC (Gill Thomas Cosman) (Fig. 2), which ensures that the treatment is consistently targeted each time. A bite plate may be used to individualize the frame for each patient and achieve reproducibility with multiple treatments (see Fig. 2; Fig. 3). Using smaller doses over many fractions reduces late side effects, such as hearing loss, when compared with single fraction RS [8].

Natural history of acoustic neuromas

When evaluating the effect of radiation therapy on the growth of ANs, the natural history of these tumors must be considered. One of the options used in the management of patients who have

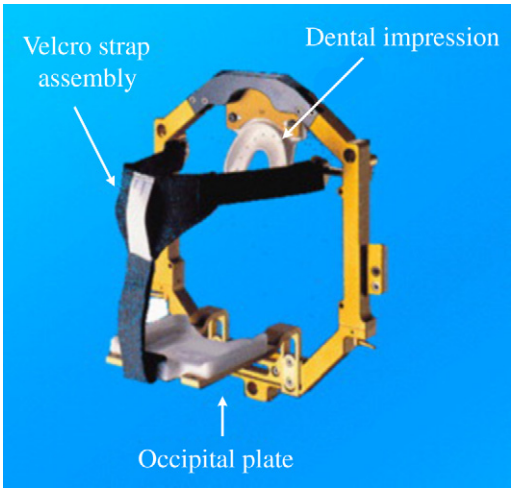

Fig. 2. A removable and reusable stereotactic device using an oral bite plate to ensure placement reproducibility.

ANs is radiologic surveillance of the tumors with repeat MRI scans. Since the introduction of gadolinium-enhanced MRI, tumors of smaller size can be detected and followed over time. A significant amount of data on the natural history of AN tumors has been collected from patients who choose this conservative option.

A review of studies on the surveillance of ANs was published by Selesnick and Johnson [9] in 1998. The authors presented a meta-analysis of 13 studies on the topic published between 1985 and 1997. In all, 571 patients across the studies

Fig. 3. This patient has been placed in the removable reusable stereotactic device using an oral bite plate to ensure placement reproducibility. The patient is positioned for treatment.

evaluated were followed for an average of 36 months. The mean diameter of tumors at the beginning of the surveillance was 11.8 mm, and 54% of the tumors (range 14%–74%) grew at an average rate of 1.8 mm per year. Slightly less than half of the patients included in the meta-analysis had no AN growth at a mean follow-up of 3 years. Among the patients whose tumor size increased ($n = 178$), the growth rate was 4 mm per year. Initial size of the tumors and the age of the patients were not found to be predictive of growth of AN.

A more recent meta-analysis published by Yoshimoto [10] in 2005 reviewed 26 studies examining the natural course of AN growth published between 1991 and 2002. In the 1340 patients included, the mean initial tumor diameter was 11 mm, and 46% (range 15%–85%) had an increase in tumor size during the mean follow-up period of 38 months (range 6–64 months). A mean growth rate of 1.2 mm per year was calculated from the 16 studies ($n = 964$) that contained this information. Eight percent of patients had a spontaneous decrease in tumor size. The author also analyzed a subgroup of 12 studies that used only MRI and not CT for tumor surveillance. In this group, 39% of tumors increased in size in the mean follow-up time of 33 months.

Since the Yoshimoto's review, Stangerup and colleagues [11] reported on 552 patients from a single institution who had ANs not associated with neurofibromatosis type 2 (NF2) and who underwent radiologic surveillance of tumors with repeated MRI scans. The data were collected for the patient population managed from 1975 to June 2005, and the mean follow-up was 43 months (range 12–180 months). Tumors were characterized as either intrameatal or extrameatal and were analyzed separately. Of the 230 intrameatal tumors, 17% grew to extend extrameatally. Growth occurred 64% of the time during the first year (growth rate, 10.32 mm/y), 23% during the second year (growth rate, 3.83 mm/y), 5% during the third year (growth rate, 2.17 mm/y), and 8% during the fourth year of observation (growth rate, 0.92 mm/y). Extrameatal tumors observed in 322 patients were defined as growing when the largest diameter increased by 2 mm and were defined as shrinking when the diameter decreased by 2 mm. In total, 70.2% of tumors remained stable, 28.9% grew, and 0.9% shrank. Sixty-two percent of growth occurred during the first year (growth rate, 4.90 mm/y), 26% occurred during the second year (growth rate, 2.79 mm/y), 10% occurred during the third year (growth rate, 1.15 mm/y), and 2% occurred during fourth year of follow-up (growth rate, 0.75 mm/y). The difference between growth of intrameatal and extrameatal ANs of 17% and 28.9%, respectively, was reported to be statistically significant. Intrameatal or extrameatal tumor growth was not observed after the fourth year of follow-up.

It is difficult to compare AN growth rates with and without radiosurgical intervention because of differences in follow-up time and methods used to report tumor size and control. Battaglia and colleagues [12] addressed the issue by comparing 111 patients followed radiologically for an average of 38 months at a single institution with data reported in the literature on radiosurgical treatment of AN. Only patients treated with the maximum marginal dose of 12 to 13 Gy administered in a single treatment with any radiosurgical modality were included in the analysis. Mainly, data from studies in which gamma knife surgery was used were represented. Only studies that reported a mean or median follow-up of 24 months were used for comparison. The natural tumor growth rate reported by the authors was 0.7 mm/y, with 18% of tumors growing faster than 1 mm/y and 13% growing faster than 2 mm/y. On average, change in size was noted at 2.2 years after surveillance was initiated. No growth during the follow-up period was noted in 50.5% of the patients. Tumor control in RS studies selected by the authors was defined as no growth more than 2 mm/y or more than 1 mm in two dimensions. Using this same definition, 87% of ANs were controlled by conservative management, a result not significantly different from when the tumors were treated with radiation.

There is some indication that AN tumors do not grow in a linear fashion. In 2000, Tschudi and colleagues [13] reported growth followed by stabilization in some of the patients whose tumors were observed over time. Charabi and colleagues [1] described a group of cases in which the tumor size was stable for an average of 19 months and then experienced a period of growth. This irregularity in the natural progression of the tumors suggests that a period of stability does not necessarily predict long-term control, whereas a period of growth does not predict continuous enlargement.

The fact that the natural history of AN growth undergoes periods of quiescence is important when trying to judge the impact of radiation therapy on these tumors.

Tumor size measurement

The current, preferred method for measuring the size of AN tumors involves the use of MRI. Accuracy and precision are important in determining the initial size of the tumor at presentation and evaluating tumor changes. The consistency of these measurements and the precision with which tumor progression can be followed have limitations.

In 2003, Slattery and colleagues [14] addressed the issue of reliability of MRI-based measurement. Factors that contribute to the quality of the scan include the MRI machine used, how the image is acquired, the training of the technician and the radiologist, whether contrast is administered, what dimension is used to measure the size of the tumor, and how much the patient moves during the scan.

A large source of variability could originate in the method of measurement. The radiologist can measure a distance by eye or use computer software. (The latter approach is considered more precise.) Studies evaluated in our review varied with respect to what constitutes the size of the tumor. Greatest diameter of the AN was commonly used. The American Academy of Otolaryngology–Head and Neck Surgery recommends that two measurements be taken: one parallel and one perpendicular to the petrous ridge. Computer algorithms allow tumor volume to be calculated to evaluate size. Each of these methods varies in its accuracy and precision.

To answer a question of how much consistency there is among data obtained from MRI scans and what is the minimum amount of change that can be detected in tumor size, Slattery and colleagues [14] performed six scans on three different MRI machines (two consecutive scans on each) for seven patients with NF2. T1-weighted post-gadolium-enhanced gradient three-dimensional sequences were used in this study. In total, 20 meningiomas and ANs were used to evaluate inter- and intrascanner reliability. The volume and the greatest diameter were measured using computer software. The authors reported that calculated tumor size was consistent across the two studies conducted on one machine and across the three machines used. They concluded that the minimal difference in tumor diameter that can be detected on an MRI is 1.1 mm, whereas the minimum reliable volume difference is 0.15 mL. The authors suggested that a more consistent protocol be used to measure tumor size in patients with AN.

This finding is important when judging the effect of radiation on acoustic tumors, because small changes in size may not be appreciated or may be overread.

Methods

For the purpose of this article, MEDLINE was searched for studies using LINAC for AN treatment. The terms "vestibular schwannoma," "acoustic neurilemmoma," "acoustic neurinoma," "acoustic neurilemoma," "acoustic schwannoma," and "acoustic neuroma" were crossed with "radiosurger*," "stereotactic radiosurger*," "linear accelerator," "LINAC," "linear accelerator-based surger*," and "X knife." (The use of [*] after a word indicates that all possible endings of the word were incorporated in the search.) Only articles published in English since 1996 were considered for analysis. The abstracts were screened to exclude articles pertaining to the use of gamma knife and other stereotactic radiation modalities. The references of selected articles were reviewed for additional relevant sources. Articles from a singles institution reporting on redundant patient populations were identified, and the more recent and complete studies were chosen for analysis.

Radiosurgery

In one of the earliest publications on LINAC RS for ANs, Chakrabarti [15] presented 11 patients in whom surgery failed to control the tumors and who were treated with stereotactic radiation. The diameter of the tumors ranged from 15 to 35 mm (mean 26 mm), and the lesions were targeted with 12.5 to 20 Gy administered to the 90% isodose contour. Ten patients were followed radiologically with repeat CT or MRI scans or both for 3 to 36 months (mean 15 months). Seven of the patients had observable necrosis in the center of the tumor 6 months after RS. During the period of 7 to 20 months after treatment, tumors decreased in size in 4 patients. No change was observed in four cases, and 1 mm increase was seen in 2 patients. Hearing was diminished in 7 patients before treatment; it was stabilized or improved in 5 of these patients, whereas 2 patients became completely deaf. Although no new facial palsy was found after RS, 4 patients experienced it before treatment. In 2 patients, their preexisting facial palsy was unchanged; it improved in 1 patient at 14 months after RS; it deteriorated

to complete facial palsy in 1 patient. In 1 patient, radiation damage to the brainstem caused imbalance [15].

The experience with LINAC stereotactic RS at Cleveland Clinic Foundation was described by Suh and colleagues [16]. Twenty-nine patients were treated in this study, with 4 suffering from NF2 and 12 having been operated on previously for ANs. The tumor volume ranged from 0.18 to 28.7 mL (median 2.1 mL). Tumors were targeted using a single isocenter in 24 cases and two isocenters in 5 cases. The treatment protocol called for a dose to the periphery that ranged from 8 to 24 Gy (median 16 Gy). Out of concern for possible damage to the brainstem, lower doses were used at first, ranging from 8 to 12 Gy. A 50% to 80% isodose line (median 80%) was used.

Patients were followed for a period of 4 to 110 months (median 49 months), during which they were seen 6 to 8 weeks after the procedure and then at 6-month intervals. The result of the treatment was local control in 28 of 29 patients defined as no increase in tumor size. Decrease in tumor size was achieved in 11 patients, and no size change was seen in 17 patients. This finding translated into an actuarial 5-year control rate of 94%. One tumor grew 41 months after the treatment.

The incidence of hearing complications was 74%, with 7 patients having a reduced level of hearing and another 7 becoming deaf. Because no audiograms were performed, the hearing data are subjective. Acute complications were noted in 2 patients and involved nausea and vomiting soon after the procedure. More serious complications included new or worsening facial numbness in 5 patients, 4 of whom experienced persistent facial numbness. Transient ataxia was noted in 3 patients (10%). New or worsening facial nerve deficit was observed in a total of 8 patients (28%) and was permanent in 7. In 1 patient, surgery to correct difficulty in closing the eye was performed. The 5-year actuarial incidence rates of trigeminal and facial neuropathy were calculated at 15% and 32%, respectively. Hydrocephalus was a problem in 2 patients, both of whom had shunts inserted. Brain stem edema on T2 images was noted on 1 patient's MRI scan and was associated with balance problems.

Statistical analysis of the results of this study did not show any association between history of previous surgery, age, sex, history of neuropathy, NF2, maximal tumor diameter, or tumor volume and the risks for long-term complications [16].

Foote and colleagues [17] described 149 patients treated with RS and analyzed the risk factors associated with this procedure. In this large study population of patients with AN, 8 patients (5.4%) had bilateral tumors associated with NF2 and 42 patients (28%) had undergone previous resection of their tumors. The mean tumor volume was 4.8 mL (range 0.3–22 mL). The number of isocenters used ranged from 1 to 11, increasing over the duration of the study, with 2 being the average. The doses of radiation administered ranged from 10 to 22.5 Gy, including only doses at increments of 2.5. A mean dose of 14 Gy was usually given to the 70% or 80% isodose line.

The results reported were based on the radiologic follow-up of 6 to 94 months (median 34 months). Control of tumor growth occurred in 93%, with 78 tumors decreasing in size and 45 tumors remaining stable. Ten lesions enlarged, giving the overall control rate at 5 years of 87% (95% CI, 76–98). Six of the patients participating in the study had to undergo surgery to excise the tumor.

In terms of complications, the risks of facial and trigeminal neuropathies 2 years after treatment were 11.8% (95% CI, 6.2–17.1) and 9.5% (95% CI, 4.5–14.3), respectively. Most of the patients who suffered these complications had transient symptoms.

The incidence of facial and trigeminal neuropathies decreased as the study continued. Of the 108 patients who were treated after January 1994, 5 patients suffered facial and 2 suffered trigeminal neuropathies. The actuarial 2-year incidence of facial neuropathy for the first 41 patients was 29%, whereas for the last 108 patients the incidence was reduced to 5%. Likewise, the risk of trigeminal neuropathy decreased from 29% to 2%. The authors suggested that this rate was representative of imaging and radiation dose planning and dose selection improvement.

Certain risk factors were shown to increase the incidence of complications. Radiation doses to the brainstem of >17.5 Gy increased the risk of facial neuropathy by 45-fold when compared with the doses <17.5 Gy. When comparing the 2-year incidence of any cranial neuropathy at doses of ≤ 12.5 Gy to doses above this value, the difference was marked at 2% and 24%, respectively. The authors also noted that having surgery before receiving radiation increased a patient's risk of developing delayed cranial neuropathy by fivefold [17].

In another study on LINAC single fraction RS for AN, Spiegelmann and colleagues [18] described 48 patients, 44 of whom were followed for 12 to 60 months (mean 32 months). Seven patients underwent prior surgery for ANs. The patients presented with maximum tumor diameters ranging from 10 to 31 mm (mean diameter 20 mm). In 40 cases the tumors were irradiated at one isocenter, 3 cases used two isocenters, and 1 case used three isocenters. Tumor margins were irradiated with an average of 14.55 Gy (range 11–20 Gy). Radiation doses ranging from 15 to 20 Gy were used for the first 2 years of the study. Later, tumors considered small and measuring <16 mm in diameter received a maximum dose of 14 Gy, whereas tumors that exceeded this size were treated with a minimum of 11 Gy at 68% to 90% isodose. This treatment was given over 20 to 45 minutes.

Based on the MRI scans obtained every 6 months earlier in the study and yearly during the last 2 years of the study, 98% of tumors were controlled. During the first year of follow-up, 11 tumors increased in size, and enlargement was combined with facial neuropathy in 8 patients. All tumors returned to smaller size at a later time. In 33 patients, tumor reduction was noted. The magnitude of shrinkage ranged from 15% to 90% and occurred at least 12 months after RS was administered. Most shrinkage occurred between 24 and 36 months. Ten tumors (23%) remained unchanged in terms of size, and 1 tumor enlarged at 48 months.

Serviceable hearing, defined as speech discrimination score of 70% or higher, was preserved in 71%. One improvement of speech discrimination score from 50% to 80% 24 months after therapy was noted.

Complications of hydrocephalus did not occur in this study. Eighteen percent of patients developed a new trigeminal neuropathy that was concomitant with facial neuropathy in all cases. In total, nine cases (24%) of facial neuropathy were reported, all of which occurred within 1 year of follow-up and experienced improvement over time. Facial weakness persisted in 3 patients. The rate of facial neuropathy, defined with the House-Brackmann scale, was 8%. The authors also noted that this rate depended on the dose of radiation administered: 5.5% of patients who received the dose of 14 Gy developed facial neuropathy, whereas patients treated with 15 to 20 Gy had a 42% incidence of neuropathy. Tumor size also had an effect. The risk of facial neuropathy was 9.5% and 54% in patients with small (0.8–3.7 mL) and large (4–11 mL) tumors, respectively. Conversely, 2 patients had improved facial nerve function after RS [18].

In the 2003 publication by Meijer and colleagues [19], single fraction RS and fractionated radiotherapy outcomes in treatment of ANs were compared. The two groups were not different with respect to tumor size (mean 2.5 cm); however, patients who received single treatment tended to be older (mean age 63 years) compared with a mean age of 43 years for the fractionated treatment group. This section describes the single fraction RS experience. Forty-nine patients were selected for the treatment with the single fraction of radiation based on their lack of teeth. The first 7 patients received a regimen of 10 Gy at 80% isodose line; the other 42 patients were treated with 12.5 Gy at 80%, with all treatments using a monoisocenter. The difference in outcomes between the patients receiving two different doses of radiation was not statistically significant. The mean follow-up for these patients was 30 months of yearly MRI scans, with tumor control defined as no increase of the diameter by 2 mm or more. The actuarial 5-year tumor control rate for RS patients was 100%.

Hearing was preserved in 75% of patients, with the data based on subjective patient reporting of perceived hearing level. The 5-year rate of facial nerve preservation was 93%, with 45 patients retaining normal function, whereas the preservation probability for the trigeminal nerve was 92%.

One patient who had undergone RS treatment developed hydrocephalus and was required to undergo an operation [19].

Two groups of patients, one treated with FSRT and the other with RS, were reported by Chung and colleagues [20] in an article entitled "Audiologic and Treatment Outcomes After LINAC-based Stereotactic Irradiation for AN." The two groups were analyzed independently, and outcomes of RS are described herein. RS was administered to 45 patients. In that group, 10 patients had prior surgery and 1 had ventriculoperitoneal (VP) shunt placed for a pre-existing hydrocephalus. The tumor diameter ranged from 4 to 34 mm (median 20 mm). All tumors were treated with a monoisocenter, with the exception of three tumors, which were treated with two isocenters. Forty-four of 45 patients received a dose of 12 Gy at 50% (3 patients) and 80% (41 patients) isodose line. One patient was treated with 15 Gy to the 80% isodose line, which

produced a tumor control rate of 100% during the follow-up period of 8 to 61 months (median 27 months).

Among the complications reported, 2 patients (4.4%) developed hydrocephalus for which VP shunts were placed. One 92-year-old patient died from this complication. Permanent mild facial numbness developed in 3 patients (7.5%), and 2 patients (4.4%) had permanent House-Brackmann grade 2 facial paresis. One patient developed an infection at the pin site of the stereotactic headring. The pons (1 patient) and the cerebellum (1 patient) became edematous because of a vasogenic process, which was mild and responded to the administration of steroids. Tumor swelling, with nonenhancing necrotic core and concurrent swelling of the tumor, caused the compression of the brainstem in 1 patient and resulted in ataxia, ipsilateral numbness at the maxillary distribution, and diplopia [20].

A 2005 study by Okunaga and colleagues [21] reported on 46 patients with unilateral ANs who were treated with LINAC RS. Of these patients, 12 (26.1%) had previously undergone resection. The tumor volume in this patient population ranged from 0.4 to 7.01 mL (median 2.29 mL) and they were targeted with one to four isocenters (median of two). Tumor margins were targeted with the median radiation dose of 14 Gy (range 10–16 Gy), and median maximal dose was 23.2 Gy (range 17–36.1 Gy). Radiation to the brainstem was limited to 10 Gy. During the 12 to 120 months of follow-up (median 56.5) with MRI studies performed every 3 to 4 months, eight tumors (19%) showed enlargement. This result was persistent and continuous in 3 patients (2 of whom had to repeat RS at 29 and 36 months), whereas in 5 patients, initial enlargement reached a plateau. No change was noted in two lesions (4.8%), whereas transient enlargement followed by shrinkage occurred in 19 patients (45.2%). Another 13 lesions (31%) shrunk directly with the minimum reduction ratio of 0.05-fold. Two tumors regrew approximately 5 years after RS.

Tumor control was achieved in 31 (73.8%) of 42 patients followed for more than 1 year, 31 (81.6%) of 38 patients followed for more than 2 years, and 18 (100%) of 18 patients followed for more than 5 years. In 11 patients, tumor size decreased more than 7 years after RS; in 5 patients tumor size decreased more than 9 years after RS. Central enhancement was lost in 37 (88.1%) of 42 tumors monitored longer than 1 year.

With respect to hearing preservation, useful hearing was maintained at Gardner-Robertson classes I or II in 66.7% of patients.

Among the procedural complications reported, 4 (7.5%) of 53 patients had hydrocephalus noted on initial visit and were treated with VP shunts and RS. Nine (21.4%) of the 42 patients monitored for longer than 1 year had ventricular enlargement. Of these patients, 3 (7.1%) required placement of a VP shunts and 4 (9.5%) improved spontaneously within 1 year of the finding. The study noted that 4.8% of patients developed new facial palsy, and new trigeminal neuropathy developed in 1 patient (2.4%) [21].

The most recently published data on the use of LINAC for treatment of ANs was found in the 2006 update of the RS experience at the Royal Adelaide Hospital. Roos and colleagues [22] reported on 65 patients with AN who underwent RS, 61 of whom had sporadic and unilateral tumors and 4 of whom had tumors associated with NF2. Six patients had prior surgeries for the tumors, which have since recurred. The median tumor diameter was 22 mm (range 11–40 mm). Radiation was given in a single dose of 12 to 14 Gy to one or two isocenters. The patients were followed with annual MRI scans and audiometry for the first 2 to 3 years and once every 2 years afterwards. The median follow-up for this study group was 48 months (range 12–134 months).

A transient enlargement and central necrosis was noted in tumors of 9 patients (16%). The median increase in size was 4 mm (range 2–5 mm) and occurred from 4 to 25 months after the treatment (median 12 months), typically persisting for 1 to 2 years. Tumor control, which was defined as a reduction or stabilization of tumor size, was achieved in 59 of the 62 patients (95%). Seventeen tumors were stable over 12 to 85 months, and 42 shrank by 2 to 12 mm (median 4 mm) over 13 to 134 months. Of the patients treated with primary RS, 98.5% did not require surgical resection of the disease, and only 1 patient required an operation.

Loss of objectively useful hearing was noted in 18 of the 34 patients with assessable, useful pretreatment levels. The loss occurred by 8 to 77 months (median 24 months). Sixteen patients (47%) maintained a useful level of hearing over 20 to 108 months (median 60 months) of follow-up. Other complications of the procedure included partial trigeminal neuropathies in 7 patients, 2 of whom also developed facial neuropathies. Of these complications, 4 were new findings, whereas

the other 3 patients had pre-existing numbness. Three cases of hydrocephalus necessitating a placement of VP shunts were reported [22].

Fractionated stereotactic radiotherapy

In a publication by Kalapurakal and colleagues [23], 19 patients with ANs were treated with FSRT. This patient group was selected for having large tumors with a mean pons-petrous diameter of 28 mm (range 15–35 mm) and a mean mid-porous transverse diameter of 35 mm (range 23–49 mm). These tumors were treated with either 36 Gy (first 6 patients) or 30 Gy (the remaining 13 patients) given in six fractions. The total dose was reduced because of ataxia experienced during the high-dose treatment by 2 patients.

The patients were followed with CT or MRI scans or both for a median of 54 months (range 34–65 months). The treatment resulted in tumor regression in 10 patients and stabilization of tumor size in the other 9. Of the 9 patients who had hearing before the procedure, 1 was noted to have an improvement and hearing was preserved at a pretreatment level in the other 8. None of the patients in this series experienced any facial or trigeminal nerve injury [23].

In 1999, Poen and colleagues [24] reported on 33 patients in whom a total of 34 AN tumors were treated with FSRT. Of these patients, 10 had NF2. Seven patients had previous operations after which the disease recurred. Tumor diameter ranged from 7 to 42 mm (median 20 mm), with 4 tumors being considered small (diameter $\leq$15 mm), 27 were moderate (16–30 mm), and 3 were classified as large ($>$30 mm). In this study, the tumors were most commonly targeted at two isocenters; however, the number of isocenters used ranged from one to four. The total radiation dose administered was 21 Gy, which was split into three fractions of 7 Gy each. Two of the first 3 patients treated received doses of 25.5 Gy and 19.5 Gy, whereas 1 patient in the study received a standard 21 Gy dose in two fractions rather than three because of a calculation error.

The patients were followed at 6-month intervals for the first 2 years and annually thereafter for a median clinical follow-up of 24 months (range 6–48 months). Tumor control was defined as no change in tumor size of 3 mm or more. Shrinkage of tumors was observed in 11 patients (34%), whereas stabilization of tumor size occurred in 20 patients (63%). One patient had an enlargement of an AN after FSRT. This patient's disease was associated with NF2, and although growth was noted at 1.8 years, regression occurred at a later time. At 2 years follow-up, 93% of patients in the study had tumor control.

Hearing was reported according to the Gardner and Robertson system and was considered useful at classes I and II. At 2 years of follow-up the rate of useful hearing preservation was 77% when NF2 patients were included in the analysis. Serviceable hearing (classes I–III) was preserved in 92% of patients with sporadic ANs and 67% of patients diagnosed with NF2 at 2 years.

The trigeminal nerve was affected in 5 patients (16%) after the treatment. In 3 of these patients the dysfunction was new, in 1 patient worsening of a pre-existing trigeminal dysesthesia was noted, and in another patient, severe ipsilateral herpes zoster in the previously affected branch was reported. In 97% of patients, facial nerve function was preserved, with a single case of injury to the nerve (House-Brackmann Grade III) 7 months after FSRT. No other treatment complications were reported [24].

Williams described the FSRT experience in 125 patients with AN, 4 of whom had previous surgical intervention for the disease and 1 of whom had a diagnosis of NF2. The tumor diameter was $<$30 mm in 111 patients and $\geq$30 mm in 14 cases. Radiation dosing was prescribed according to tumor size, with tumors $<$30 mm in diameter receiving 25 Gy in five fractions and larger tumors ($\geq$30 mm) receiving 30 Gy administered in ten fractions. Both treatments were given to the 80% isodose.

Patients were followed with MRI scans every 3 months for the first year, every 6 month after the first year, and yearly thereafter. The median follow-up time was 21 months (range 12–68 months), during which no new growth of the tumors was observed. Although the data for stabilization and shrinkage of the disease were not provided, the author reported that the tumors that did decrease in size did so by 12% and 13% in 25- and 30-Gy treatment groups, respectively.

Of the 56 patients who had audiometric follow-up for a median of a year, Gardner-Robertson classification was maintained in 26 patients, hearing worsening was noted in 20 cases, and improvement occurred in 10 patients. No difference in hearing preservation was noted across the two different radiation doses.

Two patients experienced temporary trigeminal nerve dysfunction, and none had facial nerve complications [25].

In a study by Meijer and colleagues [19], 80 dentate patients—out of a total of 129 patients involved in the study—were given FSRT for ANs. The mean tumor diameter for this group was 2.5 cm (range 0.8–3.3 cm) and was targeted with one isocenter and five doses of either 4 Gy (12 patients) or 5 Gy (68 patients) at 80% isodose line. The total radiation dose was either 20 Gy or 25 Gy. The patients were followed with yearly MRI scans for a period of 12 to 107 months (mean 35 months) and had a 94% 5-year probability of tumor control, defined as no diameter increase of 2 mm or more. In all cases tumor enlargement took place within 3 years of treatment. The actuarial 5-year facial and trigeminal nerve preservation probabilities in the fractionated treatment group ($n = 73$) were 97% and 98%, respectively. The 5-year hearing preservation probability, measured subjectively, was 61%. Radiation damage to the cerebellopontine angle was seen on MRI of 1 patient who developed gait problems 6 months after the treatment [19].

In the next study, Sawamura and colleagues [26] described 106 patients with ANs treated by FSRT. In 5 of these patients the ANs were associated with NF2. The remaining 101 patients had sporadic, unilateral solitary tumors. Twelve patients underwent surgery for their disease. Tumor diameter ranged from 3 to 40 mm (median 15.5 mm). The treatment protocol involved the administration of 40 to 50 Gy (median 48 Gy) in 20 to 25 fractions (median of 23 fractions).

The follow-up in this study was 6 to 128 months (median 45 months). MRI, neurologic, and otologic examinations were performed every 5 months for 5 years and every 12 months thereafter. The result of treatment was a 91.4% (95% CI, 85.2–97.6) 5-year actuarial rate of tumor control. Continuous tumor growth after the FSRT was seen in 3 patients (3%) who had to undergo surgery to remove the ANs.

The 5-year actuarial rate of hearing preservation (Gardner-Robertson classes I and II) was 71.7% (95% CI, 54.5–88.9). The 5-year rate of class preservation of classes I to V was 64.6% (95% CI, 53.3–75.9). These data were obtained via audiologic examinations.

Twelve patients (12%) developed hydrocephalus and required placement of a VP shunt. Among the 12 patients who had tumor resection before FSRT, 1 developed hydrocephalus as a complication of radiation treatment. When risk for hydrocephalus was analyzed with regard to tumor size, the mean size (25.5 mm) of the 11 tumors in patients who developed this complication was significantly larger than in the 86 tumors unrelated to hydrocephalus (18.2 mm). Other complications included transient facial nerve palsy (4%), trigeminal neuropathy (13.9%), and disequilibrium (16.8%). Prior existing tinnitus improved in 11 of 37 patients. Dizziness or vertigo improved in 11 of 20 [26].

In a study by Chung and colleagues [20], the group treated with FSRT contained 27 patients with ANs. Of these patients, 4 had NF2 and 1 had undergone a previous surgical resection of the tumor. They were assessed every 6 months for the first 2 years and annually thereafter with MRI and audiogram studies. The tumor diameter ranged from 7 to 37 mm (median 16 mm), and the lesions were targeted with one isocenter in 26 of 27 cases (1 patient was treated with two isocenters). Twenty-five patients were treated with 45 Gy radiation dose, which was administered in 25 fractions over 5 weeks. In 1 patient the same dose was given in 28 fractions. A 90% isodose line was used in both treatment protocols. One patient received 25 fractions for a total dose of 47.5 Gy to the 50% isodose line.

The patients in the FSRT treatment group were followed for 13 to 59 months (median 26 months), with a reported tumor control rate of 100%. Tumor progression was defined as enlargement on two consecutive MRI scans and did not occur in the study population. Hearing rate preservation was 85% at 1 year after the FSRT and decreased to 57% at 2 years follow-up. Two patients (7%) complained of transient facial numbness, and 1 patient (4%) developed transient facial paresis. One patient (4%) developed hydrocephalus that required placement of a VP shunt [20].

In a study entitled ''Stereotactic Radiotherapy for the Treatment of AN,'' Selch and colleagues [27] described 48 patients who underwent FSRT with LINAC. There was a history of partial resection of the ANs in 6 patients. The patients were followed with MRI and physical examination every 6 months for a median of 36 months (range 6–74 months). Radiologic data for at least 4 years was available for 13 patients, and for 6 patients it was available for at least 5 years. The diameter of the tumors in this study ranged from 0.6 to 4 cm (median 2.2 cm), and a single isocenter was used to target all the lesions. A total radiation dose of 54 Gy was split into in 30 fractions of 1.8 GY and was prescribed to the 90% isodose line. This dose produced tumor shrinkage of 1 to 14 mm (median 2 mm) in 12 patients (27%) at a median

of 6 months (range 6–24 months). MRI scan indicated a loss of central tumor contrast enhancement in 32 patients (67%) at a median of 6 months (range 3–12 months) after the FSRT. In 8 patients contrast enhancement returned. Increase in tumor diameter by 1 to 2 mm was observed in 12 patients (25%) at a median of 6 months (range 3–18 months). Four of these tumors decreased to original size and 2 shrank to a size smaller than the original.

Useful hearing, defined subjectively as inability to use the telephone, was preserved in 39 patients (93%), with a loss occurring in 3 patients. The 5-year actuarial probability of preserving useful level of hearing was reported at 91.4%. Facial nerve dysfunction occurred in 1 patient (2.1%) with no prior history of problems with the nerve. The actuarial 5-year probability of preserving the facial nerve function was 97.2%. One patient reported improvement of pretreatment facial nerve dysfunction. The actuarial 5-year rate of preserving trigeminal nerve function was 96.2%, with new dysfunction being noted in 1 patient (2.2%) in whom the tumor enlarged 1 mm. None of the patients treated with FSRT in this study developed hydrocephalus.

Other sequelae of FSRT treatment included worsening of tinnitus symptoms in 6 patients, 4 of whom had improvement to levels below the pretreatment levels. Pretreatment ataxia improved in 1 patient. Statistical analysis performed by the authors suggested that patient age, tumor size, and tumor volume did not relate to the outcomes after FSRT [27].

Combs and colleagues [28] reported on the use of FSRT in a population of 106 patients with ANs. Prior surgical interventions for the tumors were performed in 14 patients. Tumor diameter of $\leq$1 cm was reported in 13 patients, 1- to 2-cm tumors were found in 48 patients, 2- to 3-cm tumors were found in 30 patients, and 3- to 4-cm tumors were found in 13 patients. Two tumors had a diameter $>$4 cm. The range of target volumes as measured on MRI was 2.7 to 30.7 mL (me 3.9 mL). The total median radiation dose prescribed was 57.6 Gy and was administered in a median of 32 fractions, with 1.8 Gy per fraction.

Follow-up MRI scan was performed 6 weeks after the FSRT, then at 3- to 6-month intervals for the first 2 to 3 years, and annually afterwards. Median follow-up time was 48.5 months (range 3–172 months), and 95.3% of tumors were locally controlled on the last MRI scan. The actuarial control rate was 94.3% at 3 years and 93% at 5 years.

Hearing preservation in patients who presented with useful hearing (Gardner-Robertson classes I and II) before the FSRT ($n = 65$) was 94% at 5 years. New trigeminal neuralgia occurred in 5 patients and proved to be transient in 2 patients. Irreversible damage to the trigeminal nerve occurred in 3 of 87 patients at risk (3.4%). Pretreatment trigeminal dysesthesia resolved in 8 patients after the FSRT treatment. Two (2.3%) of the 88 patients with a normal facial nerve sustained irreversible damage [28].

In another recent study, Chan and colleagues [29] reported on 70 patients with AN treated with FSRT. Eleven of these patients were diagnosed with NF2, and 21% had previous surgeries for AN tumors. The median size of the tumors in this patient population was 2.4 mL (range 0.05–21.1 mL), and the lesions were targeted at one isocenter. A total dose of 54 Gy was administered in 30 fractions of 1.8 Gy each to the 95% isodose line.

The patients were followed for a median of 45.3 months after the treatment. The range of follow-up periods was not provided by the authors. Of the 70 patients, radiologic data were available for 68; data showed decrease in central enhancement at median of 7 months in 46% of all tumors treated with FSRT. Tumor shrinkage was observed in 53 cases, with actuarial 3- and 5-year size decrease in 36% and 62%, respectively. Tumor enlargement was noted in 4 patients occurring 2 years after treatment in all cases. At 3 and 5 years, the actuarial tumor control rates were 100% and 98%, respectively.

Because hearing preservation was assessed using a subjective scale, the data from this study are not used in the overall analysis.Among the complications reported, one patient had a change in facial weakness from House-Brackmann grade 2 to grade 5. The 5-year actuarial probability of facial nerve function preservation was 99%. Eight cases of facial twitching and spasming (defined as facial hyperfunction) were reported. Two cases of transient facial numbness were recorded, with the actuarial 5-year trigeminal nerve preservation rate of 96%. Statistical analysis performed by the authors indicated that previous tumor resections increased the risk of trigeminal neuropathy [29].

Data summary

Tumor control

When comparing microsurgical treatment of AN tumors to radiation therapy, it is important to

Table 1
Tumor control after stereotactic radiosurgery with the linear accelerator

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mos)	Tumor size	Result	% Grew	% Stable	% Shrank
Florida	2001	133	1	10–22.5	6–94 (median 34)	0.3–22 mL (mean 4.8 mL)	87% 5-year actuarial control	7	34	59
Adelaide	2006	62	1	12–14	12–134 (median 48)	11 mm–40 mm	95% control = no increase of $\geq$2 mm	4.8	27.4	67.7
Nagasaki	2005	53	1	Margins: 10–16 Max: 17–36.1	12–120 (median 56.5)	0.4–7.01 mL (median 2.29 mL)		19	4.8	76.2 (after transient enlargement in 45.2)
		42	—		12		73.8% control in 42 patients	26.2	—	
		38	—		24		81.6% control in 38 patients	18.4	—	
		18	—		60		100% control in 18 patients	0	—	
Amsterdam	2003	49	1	10 & 12.5	12–107 (mean 30)	8–38 mm (mean 25)	100% 5-year actuarial control	0	100%	
Vancouver	2004	45	1	12	8–61 (median 27)	4–34 mm (median 20 mm)	100% control rate	0	100%	
Tel Hashomer	2001	44	1	11–20	12–60 (mean 32)	10–31 mm (mean 20 mm)	98% control rate	2	23	75 (by 15%–90%)
Cleveland	2000	29	1	8–24	4–110 (median 49)	0.18–28.7 mL (median 2.1 mL)	94% 5-year actuarial control	3	59	38
London	1996	10	1	2.5–20	3–36 (mean 15)	15–35 mm (mean 26 mm)	80% control rate	20 (1 mm)	40	40

Table 2
Tumor control after linear accelerator fractionated stereotactic radiotherapy

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result	% Grew	% Stable	% Shrank
Baltimore	2002	125	5 10	25 30	12–68 (median 21)	<30 mm: 111 ≥30 mm: 14	100% control (no new growth)	0	100	
Heidelberg	2005	106	32	57.6	3–172 (median 48.5)	0–10 mm: 13 11–20 mm: 48 21–30 mm: 30 31–40 mm: 13 >40 mm: 2	94.3% 3-year actuarial control; 93% 5-year actuarial control	4.7	95.3	
Sapporo	2003	101	20–25	40–50	6–128 (median 45)	3–40 mm (median 15.5 mm)	91.4% 5-year actuarial control	3	97	
Amsterdam	2003	80	5	20 or 25	12–107 (mean 35)	8–33 mm (mean 25 mm)	94% 5-year actuarial control = no increase in the largest diameter >2 mm	N/A	N/A	N/A
Boston	2005	70	30	54	median 45.3	0.05–21.1 mL (median 2.4 mL)	100% 3-year actuarial, 98% 5-year actuarial control rate	6	18	76
Los Angeles	2004	48	30	54	6–74 (median 36)	6–40 mm (median 22 mm)	100% 5-year actuarial control in 6 patients	12.5 (1–2 mm)	60.5	27 (1–14 mm, median 2 mm)
Stanford	1999	33	3	21	24	7–42 mm (median 20 mm)	93% control at 2 years = no increase of >3 mm	3	63	34
Vancouver	2004	27	25	45	13–59 (median 26)	7–37 mm (median 16 mm)	100% control = no enlargement on two consecutive MRIs	0	100	
Philadelphia	1999	19	6	30 or 36	24–65 (median 54)	23–49 mm (mean 35 mm)	100% control	0	47	53

Table 3
Hearing preservation after stereotactic radiosurgery

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Adelaide	2006	34	1	12–14	12–134	11–40	47% useful hearing preservation
Tel Hashomer	2001	13	1	11–20	12–60	10–31 mm (mean 20 mm)	71% hearing preservation rate; serviceable hearing, defined as speech-discrimination score of $\geq$70%
Nagasaki	2005	9	1	17–36.1	12–120	0.4–7.01 mL (median 2.29 mL)	66.7% patients maintained useful hearing (GR I and II)
London	1996	7	1	12.5–20	3–36	15–35 mm (mean 26 mm)	Stabilized or improved in 5, and deteriorated to complete deafness in 2

Table 4
Hearing preservation after fractionated stereotactic radiotherapy

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Sapporo	2003	106	20–25	40–50	6–128 (median 45)	3–40 mm (median 15.5 mm)	71.7% GR I and II preservation
Heidelberg	2005	65	32	57.6	3–172 (median 48.5)	0–10 mm: 13 11–20 mm: 48 21–30 mm: 30 31–40 mm: 13 >40 mm: 2	94% 5-year actuarial rate of hearing preservation (GR I and II)
Baltimore	2002	56	5 10	25 30	12–68 (median 21)	<30 mm: 111 $\geq$30 mm: 14	46.4% maintained GR class, hearing worsened in 35.7%, and improved in 17.8%
Stanford	1999	33	3	21	24	7–42 mm (median 20 mm)	92% serviceable hearing (GR I-III) preservation rate at 2 years for patients with sporadic AN;67% for patients who have NF2
Vancouver	2004	22	25	45	12 24	7–37 mm (median 16 mm)	85% (GR I and II) 57%
Philadelphia	1999	9	6	30 or 36	24–65 (median 54)	23–49 mm (mean 35)	100% preservation; one case of improvement

Table 5
Facial nerve (VII) preservation after stereotactic radiosurgery

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Florida	2001	41 108	1	10–22.5	6–94	0.3–22 mL (mean 4.8 mL)	29% 2-year actuarial incidence of facial neuropathy 5% 2-year actuarial incidence of facial neuropathy; 11.8% overall incidence at 2 years (mostly transient)
Adelaide	2006	57	1	12–14	12–134	11–40	3.5% had mild neuropathy
Amsterdam	2003	49	1	10 and 12.5	12–107 (mean 30)	8–38 mm (mean 25)	93% 5-year rate of facial nerve preservation
Vancouver	2004	45	1	12	8–61	4–34 mm (median 20 mm)	4.4% developed permanent House-Brackmann Grade 2 facial paresis
Nagasaki	2005	42	1	17–36.1	12–120	0.4–7.01 mL (median 2.29 mL)	4.8% had new facial palsy
Tel Hashomer	2001	37	1	11–20 14 15–20	12–60	10–31 mm (mean 20 mm) 0.8–3.7 4–11	24% of transient new facial neuropathy; 8% had persistent facial weakness; 2 patients had facial nerve improvement; 5.5% developed facial neuropathy 42% developed facial neuropathy 9.5% facial neuropathy 54% facial neuropathy
Cleveland	2000	29	1	8–24	4–110	0.18–28.7 mL (median 2.1 mL)	28% had deficit, permanent in 24%; 32% 5-year actuarial rates of facial neuropathy
London	1996	11	1	12.5–20	3–36	15–35 mm (mean 26 mm)	0% new facial nerve palsy; 2 of 4 cases of old facial palsy were unchanged; 1 of 4 improved (at 14 months); 1 of 4 deteriorated to complete facial palsy

Table 6
Facial nerve (VII) preservation after fractionated stereotactic radiotherapy

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Baltimore	2002	125	5 10	25 30	12–68 (median 21)	$<$30 mm: 111 $\geq$30 mm: 14	0% damage
Sapporo	2003	106	20–25	40–50	6–128 (median 45)	3–40 mm (median 15.5 mm)	4% developed transient facial palsy
Heidelberg	2005	88	32	57.6	3–172 (median 48.5)	0–10 mm: 13 11–20 mm: 48 21–30 mm: 30 31–40 mm: 13 $>$40 mm: 2	2.3% sustained irreversible damage
Amsterdam	2003	73	5	20 or 25	12–107 (mean 35)	8–33 mm (mean 25 mm)	97% 5-year actuarial nerve preservation
Boston	2005	70	30	54	median 45.3	0.05–21.1 mL (median 2.4 mL)	1.5% facial weakness (House-Brackman II progressing to V); 99% 5-year actuarial facial nerve preservation
Los Angeles	2004	48	30	54	6–74	6–40 mm (median 22 mm)	2.1% had new facial palsy (House-Brackmann V); improvement from V to IV in one patient
Vancouver	2004	45	1	12	8–61	4–34 mm (median 20 mm)	4% transient facial paresis
Stanford	1999	33	3	21	6–48	7–42 mm (median 20 mm)	3% facial nerve injury (House-Brackmann Grade III)
Philadelphia	1999	16	6	30 or 36	24–65 (median 54)	23–49 mm (mean 35 mm)	0% damage

Table 7
Trigeminal nerve (V) preservation after stereotactic radiosurgery

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Florida	2001	41 108	1	10–22.5	6–94	0.3–22 mL (mean 4.8 mL)	29% 2-year actuarial risk of trigeminal neuropathy 2% 2-year actuarial risk of trigeminal neuropathy; 9.5% overall incidence at 2 years (mostly transient)
Adelaide	2006	62	1	12–14	12–134	11–40 mm	11.3% mild developed neuropathy
Nagasaki	2005	53	1	Margins: 10–16 Max: 17–36.1	12–120 (med 56.5)	0.4–7.01 mL (median 2.29 mL)	2.4% developed trigeminal neuropathy
Amsterdam	2003	49	1	10 and 12.5	12–107 (mean 30)	8–38 mm (mean 25)	92% 5-year nerve preservation
Vancouver	2004	45	1	12	8–61	4–34 mm (median 20 mm)	7.5% developed permanent mild facial numbness
Tel Hashomer	2001	44	1	11–20	12–60	10–31 mm (mean 20 mm)	18% developed neuropathy
Cleveland	2000	29	1	8–24	4–110	0.18–28.7 mL (median 2.1 mL)	17.2% new facial numbness, permanent in 13.8%; 15% 5-year actuarial rate of trigeminal neuropathy

keep in mind the different goals of these therapeutic modalities. The goal of microsurgery is to resect the tumor and leave little or no disease behind. Radiation therapy, however, aims to arrest the growth of the tumor or cause it to become smaller. In all the studies reviewed, successful control was defined as no enlargement of the tumor on serial MRI scans. Success of surgical treatment cannot necessarily be equated with the success of RS or FSRT.

As described in the section on natural history of AN in this article, AN tumors are slow-growing tumors that may be stable for periods of time. This nonlinear pattern of growth necessitates that patients be followed for long periods of time after radiation therapy to assess the true efficacy of this procedure. The minimum follow-up for patients treated with RS reported in the analyzed series was 3 months, with several other studies reporting minimum follow-up time less than 1 year. Patients treated with FSRT had a minimum follow-up time of 6 months (in two studies). These follow-up periods are unacceptable, because a lack of tumor growth during this period is not equivalent to the ultimate success of therapy. Although most studies for RS and FSRT had a median follow-up of more than 2 years and a maximum follow-up of 5 years and more, only one study [21] separated patients based on the length of follow-up, therefore strengthening the data. It would be more valuable to know the results of treatment at longer follow-up periods rather than the control rate across patients followed for various lengths of time. Lack of such data weakens any conclusions that can be made on the subject.

Reported tumor control after stereotactic RS ranged from 73.8% to 100%, whereas control in patients treated with FSRT was 91.4% to 100%. Stabilization of tumor growth in patients treated with RS ranged from 4.8% to 59%. Shrinkage was observed in 38% to 76.2% of tumors irradiated with a single dose, whereas 0% to 26.2% increased in size (Table 1). FSRT patients experienced stabilization in 18% to 63% of cases, shrinkage in 34% to 76% of cases, and tumor growth in 0% to 12.5% of cases (Table 2). Given the limitations stated previously, this finding suggests that fractionation of radiation treatment leads to better control of AN. Tumors targeted with a single dose of radiation decreased in size more often than tumors that underwent FSRT; however, they also grew more often.

Tremendous variability in the total amount of radiation (total Gy) administered is seen across

Table 8
Trigeminal nerve (V) preservation after fractionated stereotactic radiotherapy

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Baltimore	2002	125	5 10	25 30	12–68 (median 21)	<30 mm: 111 ≥30 mm: 14	1.6% temporary dysfunction
Sapporo	2003	106	20–25	40–50	6–128 (median 45)	3–40 mm (median 15.5 mm)	13.9% neuropathy
Heidelberg	2005	87	32	57.6	3–172 (median 48.5)	0–10 mm: 13 11–20 mm: 48 21–30 mm: 30 31–40 mm: 13 >40 mm: 2	5.7% total, 3.4% irreversible
Amsterdam	2003	73	5	20 or 25	12–107 (mean 35)	8–33 mm (mean 25 mm)	98% 5-year actuarial preservation
Boston	2005	70	30	54	median 45.3	0.05–21.1 mL (median 2.4 mL)	3% developed transient facial numbness; 96% 5-year actuarial trigeminal nerve preservation
Los Angeles	2004	48	30	54	6–74	6–40 mm (median 22 mm)	2.2% experienced new dysfunction
Stanford	1999	33	3	21	6–48	7–42 mm (median 20 mm)	16% nerve injury; new dysfunction in 9.7%; worsening of old symptoms in 6.3%
Vancouver	2004	27	25	45	13–59 (median 26)	7–37 mm (median 16 mm)	7% transient facial numbness
Philadelphia	1999	15	6	30 or 36	24–65 (median 54)	23–49 mm (mean 35)	0% damage

Table 9
Incidence of hydrocephalus after stereotactic radiosurgery

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Adelaide	2006	65	1	12–14	12–134	11–40	4.6%
Nagasaki	2005	53	1	17–36.1	12–120	0.4–7.01 mL (median 2.29 mL)	7.5%
Amsterdam	2003	49	1	10 and 12.5	12–107 (mean 30)	8–38 mm (mean 25)	2%
Tel Hashomer	2001	48	1	11–20	12–60	10–31 mm (mean 20 mm)	0%
Vancouver	2004	45	1	12	8–61	4–34 mm (median 20 mm)	4.4%
Cleveland	2000	29	1	8–24	4–110	0.18–28.7 mL (median 2.1 mL)	6.9%

the analyzed studies. In general, an increase in the total radiation dose provides better tumor control while elevating the probability of complications associated with treatment.

Hearing preservation

The location of AN tumors jeopardizes hearing. Many patients present with varying degrees of hearing loss, which unfortunately is not restored. In general, the best outcome after resection or irradiation of an AN is to maintain the pretreatment hearing level. In analyzing the data reported in the literature, we looked for the rates of hearing preservation measured on an objective scale. This rate involved a pre- and postradiation auditory examination. Any subjectively defined data were not included in our analysis. The probability rate of useful hearing preservation in patients treated with RS ranged from 47% to 71%, with useful hearing defined as Gardner-Robertson classes I and II (Table 3). This rate is based on a limited population size, with 56 cases reported over three studies [18,21,22]. Hearing preservation rate after FSRT was much more favorable, ranging from 57% to 100% across six studies (Table 4). One study reported an improvement of hearing in 17.8% (ten cases) [25].

Other complications

The complications of radiation therapy for AN that were cited most often in the studies evaluated in this article included facial and trigeminal nerve neuropathy and hydrocephalus. Facial nerve dysfunction was reported in 0% to 54% of patients whose tumors were treated with RS (Table 5). This large range is partly caused by the heterogeneity of treatment protocols and tumor sizes. When facial nerve complications were stratified according to radiation dose and tumor size, large tumors exposed to the most radiation were most likely to be associated with neuropathy [18]. Fractionated radiation treatment was associated with a much smaller incidence of facial nerve injury, ranging from 0% to 4% (Table 6).

A similar trend was found with regard to complications involving the trigeminal nerve. Trigeminal nerve dysfunction was seen in 2.4% to

Table 10
Incidence of hydrocephalus after fractionated stereotactic radiotherapy

City	Year	N	No. of sessions	Total dose (Gy)	Follow-up (mo)	Tumor size	Result
Sapporo	2003	101	20–25	40–50	6–128	3–40 mm (median 15.5 mm)	12%
Amsterdam	2003	80	5	20 or 25	12–107 (mean 35)	8–33 mm (mean 25 mm)	0%
Los Angeles	2004	48	30	54	6–74	6–40 mm (median 22 mm)	0%
Stanford	1999	33	3	21	6–48	7–42 mm (median 20 mm)	0%
Vancouver	2004	27	25	45	13–59	7–37 mm (median 16 mm)	4%

29% of patients treated with RS (Table 7) and in 0% to 16% of FSRT patients (Table 8). Complication of hydrocephalus was seen in 0% to 7.5% of RS patients (Table 9) and 0% to 12% of FSRT patients (Table 10). In most cases, an operation for VP shunt placement was required.

Summary

The review of literature on the use of LINAC stereotactic RS and FSRT in the treatment of AN leads us to conclude that these modalities are essentially safe. Although the incidence of therapies resulting in the most common complications—including facial and trigeminal nerve neuropathy and hydrocephalus—is low, hearing preservation after irradiation of the tumor is poor. The efficacy of these modalities to control tumor growth is still in question. Larger study populations with longer follow-up time are needed. In general, FSRT is better than RS in terms of tumor control and reduced complication rates.

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