LONG-TERM OUTCOME OF STEREOTACTIC RADIOSURGERY (SRS) IN PATIENTS WITH ACOUSTIC NEUROMAS

STEPHANIE E. COMBS, M.D.,*† CHRISTOPH THILMANN, M.D.,*† JÜRGEN DEBUS, M.D., PH.D.,*† AND DANIELA SCHULZ-ERTNER, M.D.*†

*Department of Radiation Oncology, University of Heidelberg, Heidelberg, Germany; and †Department of Radiation Oncology, German Cancer Research Center, Heidelberg, Germany

Purpose: To evaluate the effectiveness and long-term outcome of stereotactic radiosurgery (SRS) for acoustic neuromas (AN).

Patients and Methods: Between 1990 and 2001, we treated 26 patients with 27 AN with SRS. Two patients suffered from neurofibromatosis type 2. Before SRS, a subtotal or total resection had been performed in 3 and in 5 patients, respectively. For SRS, a median single dose of 13 Gy/80% isodose was applied.

Results: The overall actuarial 5-year and 10-year tumor control probability in all patients was 91%. Two patients developed tumor progression after SRS at 36 and 48 months. Nineteen patients (73%) were at risk of treatment-related facial nerve toxicity; of these, 1 patient developed a complete facial nerve palsy after SRS (5%). A total of 93% of the lesions treated were at risk of radiation-induced trigeminal neuralgia. Two patients (8%) developed mild dysesthesia of the trigeminal nerve after SRS. The hearing preservation rate in patients with useful hearing before SRS was 55% at 9 years.

Conclusion: Stereotactic radiosurgery results in good local control rates of AN and the risk of cranial nerve toxicities is acceptable. As toxicity is lower with fractionated stereotactic radiotherapy, SRS should be reserved for smaller lesions. © 2006 Elsevier Inc.

INTRODUCTION

Acoustic neuromas (AN) occur with an incidence of 1 per 100,000 of the population and are benign tumors commonly arising from the vestibular branch of the eighth cranial nerve (1). They present as extracanalicular tumors, intracanalicular tumors, or within the cerebellopontine angle. Generally, one can observe a very slow growth pattern with an increase in diameter of no more than 1 mm per year (1).

In recent years, several treatment options for patients with AN have been established. Microsurgery is considered the standard approach, offering both immediacy of tumor removal and low rates of recurrences (2–5). However, surgery might be associated with a marked incidence of cranial and noncranial nerve morbidities, although modern microsurgical techniques have significantly decreased morbidity and mortality (3, 6–9).

Conventional radiation therapy has been employed to prevent local tumor progression in cases of recurrent or residual tumors (10). Modern radiotherapeutic treatment options such as fractionated stereotactic radiotherapy (FSRT) offer a noninvasive treatment with tumor control rates comparable to microsurgery, but with a higher rate of hearing preservation and preservation of facial and trigeminal nerve function (11–13).

Stereotactic radiosurgery (SRS) has been shown to be another noninvasive treatment alternative to microsurgical resection or FSRT in patients with smaller AN (1, 14, 15). It can be performed as gamma knife radiosurgery or as linac-based radiosurgery. Leksell and Norén were the first to report very favorable outcomes in patients treated with gamma knife radiosurgery in the 1960s (16, 17). The technique of SRS aims at focusing multiple beams of radiation on a defined target (17). With the subsequent introduction of linear accelerators (linac) dedicated to stereotactic treatments, linac-based SRS has become a cost-effective alternative to gamma knife radiosurgery. For both radiosurgical treatment options, complications include hearing loss, facial weakness and numbness, tinnitus, imbalance, headache, dysesthesia, dysphagia, cystic necrosis, and hydrocephalus (18). Results obtained with SRS in the treatment of AN are comparable with those achieved with gamma knife radiosurgery with respect to local control and complications (13, 19–22). The main advantage of SRS as compared with FSRT is the application of the therapeutic dose in a
single fraction, minimizing treatment times and potential hospitalization times. Especially older patients or patients with a number of comorbidities are likely to benefit from the reduced treatment time.

The present analysis reports on our results obtained in 26 patients with AN treated with SRS in our institution with special respect to long-term treatment outcome including local tumor control and radiation-induced side effects.

PATIENTS AND METHODS

Between 1990 and 2000, we treated 26 patients with SRS for 27 AN at a single institution. All patients were followed prospectively and no patient was lost to follow-up.

Eighteen patients were female and 8 patients were male. The median age at SRS was 64 years (range, 39–83 years). The median age at primary diagnosis of the AN was 64 years (range, 38–83 years), with a median time between diagnosis and SRS of 5 months (range, 1–72 months).

The AN was localized on the right vestibular nerve in 13 patients, on the left vestibular nerve in 11 patients, and bilaterally in 2 patients. Two patients suffered from neurofibromatosis type 2, and of these 2 patients, 1 patient presented with bilateral AN. In patients with bilateral AN, only the side treated with SRS was included into this analysis.

Twenty-one tumors were localized intra- and extracanaliculary, and two and four tumors were localized intracanaliculary or extracanaliculary only. The median tumor diameter was 15 mm (range, 2–28 mm). The tumor size distribution according to the largest diameter can be found in Fig. 1a.

Before SRS, in 3 patients a subtotal resection and in 5 patients a total resection of the AN had been performed. In these cases SRS was performed as salvage therapy for recurrent or progressive tumors. In 1 patient, a neurosurgical resection of a contralateral AN had been performed.

All patients were treated using a single, high-dose radiation treatment as described previously (23). For treatment planning and for subsequent SRS, an individual precision head mask system made of Scotch cast was manufactured for each patient (24, 25). This fixation system allows a positioning accuracy of 1–2 mm. With the mask system attached to a stereotactic localization system attached to the base frame, contrast-enhanced computed tomography and magnetic resonance imaging scans were acquired with a slice thickness of 3 mm (26, 27). After stereotactic image fusion, the target volume and organs at risk were defined on each slice of the three-dimensional data cube using the three-dimensional treatment planning system STP (Stryker-Leibinger, Freiburg, Germany) or the VIRTUOS planning program (dkfz, Heidelberg, Germany). The planning target volume was defined as the area of contrast enhancement on T1-weighted magnetic resonance imaging including a 1–2 mm safety margin for possible patient mis-alignment. Radiosurgery was delivered with circular collimators or, for irregularly shaped AN, with a multileaf collimator (leaf width, 1.5 mm at isocenter).

The prescribed dose was chosen after evaluation of the dose–volume histogram with respect to the size of the planning target volume, hearing evaluation, and the localization of the AN. A median single dose of 13 Gy (range, 11–20 Gy) was prescribed to the 80% isodose (Fig. 1b).

All patients received 20 mg dexamethasone 1 h before and 6 h after radiosurgery, together with H2-antihistamine for stomach ulcer prophylaxis.

All patients were seen 6 weeks after SRS for a first follow-up visit, and thereafter in 3- to 6-months intervals for the first 2–3 years. Thereafter, yearly follow-up examinations were performed. All follow-up visits included a thorough neurologic assessment and a contrast-enhanced magnetic resonance imaging scan. Hearing evaluation was recommended to be performed by the patients’ home otolaryngologist on a regular basis and was available to evaluate hearing function. For the evaluation of SRS-related side effects and the long-term outcome, a detailed questionnaire was sent out to all patients.

Pre- and posttreatment hearing was classified according to the Gardner-Robertson modification of the classification system of Silverstein (28). For hearing classification, we included information from the patients’ charts, hearing evaluations performed before and after radiotherapy by the patients otolaryngologists, or data collected from the primary care physicians and the patient questionnaire.

Useful hearing in the treated ear was considered if patients qualified as Gardner Robertson Class I or II.

Local control and hearing preservation probability were calculated using the Kaplan-Meier method. For intergroup differences, the log–rank test was applied. All statistical analyses were performed using Statistica 6.0 (StatSoft, Hamburg, Germany).

RESULTS

Local tumor control

The overall actuarial 5- and 10-year tumor control probability in all patients was 91% (Fig. 2). In the group consisting of patients with sporadic AN, local control was 96%
at 5 and 91% at 10 years, respectively. In patients suffering from neurofibromatosis type 2 (NF-2) \( (n = 2) \), local tumor control was 100% at 10 years. This difference was not significantly different at \( p = 0.84 \) (log–rank). We analyzed the difference in local tumor control with regard to previously performed neurosurgical intervention. For previously untreated patients, local tumor control was 94% at 5 and 10 years after SRS as compared to 88% at 5 and 10 years in the patient group that had received prior neurosurgical resection. This difference was not significant at \( p = 0.54 \) (log–rank).

Two patients developed tumor progression after SRS at 36 and 48 months. Of these 2 patients, 1 patient had undergone neurosurgery before SRS and tumor progression.

**Treatment-related toxicity**

Stereotactic radiosurgery was well tolerated in all patients. No severe acute toxicity > Common Toxicity Criteria Grade 2 occurred.

The median follow-up time after SRS was 110 months (range, 30–175 months).

During the follow-up period, 1 patient developed a radiologically confirmed necrosis of the AN and a small necrotic lesion within the cerebellum with peripheral contrast enhancement. In another patient an intermittent disruption of the blood–brain barrier developed 3 months after SRS that persisted until 41 months after SRS and disappeared thereafter.

No other severe long-term toxicities > Common Toxicity Criteria degree 2 could be observed.

At the time point of SRS, 8 patients presented with complete or incomplete facial nerve palsy. Of these patients, 5 had received a complete neurosurgical resection before RT and received SRS for tumor progression. Three patients presented with facial nerve palsy without any prior treatment. Of all 27 lesions treated with SRS, 19 (73%) were at risk for treatment-related facial nerve toxicity.

One patient of the 19 patients at risk developed a complete facial nerve palsy after SRS (5%). Three patients intermittently developed incomplete facial nerve palsy on the side of the AN treated with SRS (15%).

Two patients presented with symptoms of typical trigeminal neuralgia before radiotherapy. One of the 2 patients had undergone a total neurosurgical resection of the AN and received SRS for tumor progression. The second patient without any prior treatment of the AN experienced pain relief during follow-up after SRS.

A total of 93% of the lesions treated (25 out of 27) was at risk of developing radiation-induced trigeminal neuralgia. Two of these patients (8%) developed mild dysesthesia of the trigeminal nerve after SRS, 1 of whom had also developed necrosis of the AN and within the cerebellum after SRS.

**Hearing preservation**

Hearing impairment was the leading symptom for the diagnosis of AN or aggravated during a surveillance period. At the time of referral, 35% of patients presented with non-serviceable hearing, which means hearing loss or any testable hearing that was not useful.

Seventeen patients out of 26 (65%) presented with useful hearing before SRS and were at risk of developing treatment-related hearing loss after radiotherapy. New hearing loss or hearing impairment considered as no longer useful after SRS was found in 5 patients. The hearing preservation rate in patients with useful hearing before SRS was 55% at 9 years after SRS (Fig. 3).

Hearing preservation rates were not significantly different in patients with sporadic AN as compared with patients with NF-2 \( (p = 0.72, \text{log–rank}) \). Additionally, there was no statistical difference in hearing preservation with regard to tumor size \( (<1 \text{ cm vs. } \geq 1 \text{ cm}; p = 0.4) \) and tumor size in combination with the prescribed dose \( (<1 \text{ cm and } <15 \text{ Gy vs. all other patients}; p = 0.4, \text{log–rank}) \). Previously performed neurosurgical resection did not influence the hearing preservation rate in patients presenting with useful hearing \( (p = 0.4, \text{log–rank}) \).

In patients with non-serviceable hearing before SRS, residual hearing function, which was, however, not useful, was preserved in 50% at 7 years after SRS.
DISCUSSION

Over the past decades, several treatment options for patients with AN have emerged. Microsurgery, SRS, and FSRT have an established role in the treatment of AN, and physicians as well as patients are faced with the choice between these treatment alternatives. However, each procedure is associated with certain benefits for the patient as well as with a specific toxicity spectrum that has to be considered in the choice of the optimal treatment for each individual patient. Tumor size, hearing level on the affected side, and the patient’s preference should be taken into account before opting for any treatment modality.

In general, observation of the diagnosed AN might be indicated in a number of situations, especially in elderly and/or medically unfit patients without progressive neurologic symptoms or long-tract, brainstem, or cerebellar signs apparent on clinical presentation. Additionally, in patients with bilateral AN with perhaps only residual hearing on the affected side, or any patients with deafness on the contralateral ear, as well as patients generally refusing treatment, a wait-and-see strategy can be justified.

However, microsurgery is still considered the standard approach for the treatment of AN. In principle, there are three different microsurgical approaches: the middle fossa, translabyrinthine, and the suboccipital approach. Each surgical approach is associated with a distinct risk for cranial nerve damage, including hearing loss and loss of facial and trigeminal nerve function (29–31). The middle and posterior fossa approaches are useful for hearing preservation surgery, especially in smaller tumors, but are associated with a higher risk for facial nerve palsies (9, 32–34). Hearing preservation rates of 31–59% were reported for these techniques (29, 30, 35, 36). For the suboccipital approach, hearing preservation rates from 11% to 83% were reported (34, 37–39). However, although useful for the resection of smaller or medium sized tumors, the translabyrinthine approach does not allow hearing preservation.

As a noninvasive alternative to surgery, a number of radiotherapeutic techniques have evolved and have been established for the treatment of AN, providing excellent local tumor control as compared with surgery, however, with a smaller risk of therapy-related side effects to the cranial nerves.

Stereotactic radiosurgery, a concept introduced by Leksell in 1951, has been shown to be a viable and effective alternative therapy for patients with AN (19, 22, 40, 41).

It permits the application of a high single dose to a stereotactically defined treatment volume while enabling a steep dose falloff around the target volume, sparing normal tissue in close vicinity (4, 42). SRS can be delivered by a 60Co gamma knife or a linac. The gamma knife was first used for AN by Leksell in 1969 (17). A main advantage of SRS is the application of an effective treatment dose in a single session, resulting in minimal treatment duration and hospitalization times. This can be extremely useful in treating elderly patients, patients with a number of comorbidities, or patients refusing to accept the necessity for week-long therapies. Additionally, patients with claustrophobia or panic because of the fixation device can profit from this single-dose treatment, because anxiolytic medication only has to be administered for treatment planning and thereafter for the single treatment session. However, despite the numerous benefits, SRS is associated with an increased risk for loss of hearing function and for treatment-related toxicity to the facial and trigeminal nerves as compared with fractionated RT regimens.

Several studies evaluating the effectiveness of SRS in the management of AN have shown that local tumor control is highly comparable to microsurgery, Karpinos et al. could show tumor control rates of 91% for SRS as compared with 100% achieved by microsurgery (18). Several other studies have reported similar control rates of 86–100% at 2–12 year follow-up for patients treated with SRS (12, 43–47). Generally, local control rates are higher for smaller tumors than for large lesions treated with SRS. Forster et al. could show that AN greater than 3 cm had a control rate of 33% and tumors measuring 2–3 cm showed a growth control of 86%. Tumors of 2 cm could be controlled in 89% (48). For microsurgery, local tumor control correlated strongly with the amount of tumor removed, with control rates of up to 100% after total resections, and of 45–95% for subtotal resections (31, 49, 50). In our study, local tumor control for patients with sporadic AN was 96% and 91% at 5 and 10 years, respectively. Tumor size in our patient group did not have a significant impact on local control after SRS. For FSRT, similar local tumor control rates of 91% to 100% have been reported (51–53).

However, with respect to cranial nerve toxicity, patients are likely to profit from fractionated treatment schemes.

With FSRT, treatment-related toxicity to the facial nerve of 0–3% can be found in the literature (14, 51–57). With microsurgery, the rate of cranial nerve toxicity depends strongly on the size of the AN. Small tumors are associated with 0–6% facial neuropathies; in medium-sized tumors, rates of 8–24% of facial neuropathies can be observed; and in patients with large tumors, facial palsy rates of 40% to 80% could be found (31, 58). Treatment of AN with SRS may lead to facial nerve toxicity rates of 0–23% as reported in different studies (12, 13, 16, 18, 52, 59, 60). In a study published by Karpinos et al., the rate of facial neuropathy immediately after treatment was 0% after SRS vs. 35% after microsurgery and 6.1% vs. 35.3% at long-term follow-up, respectively (18). These results were also supported by Pollack et al., who reported higher postsurgical toxicity to the facial nerve as compared with SRS. In the present study, the rate of facial nerve neuropathy after SRS was 5% for complete facial palsy after SRS. These results support previous data indicating that facial nerve toxicity is comparably low with SRS. However, by implementing a fractionated RT scheme toxicity rates can be further reduced as indicated above.

With respect to trigeminal nerve function, toxicity rates of 4–27% after SRS are reported in the literature. Several
studies indicate that the risk for trigeminal neuropathy is higher after microsurgery. Karpinos et al. could show that immediate postoperative trigeminal toxicity was 17% after microsurgery as opposed to 0% after SRS, and 22% vs. 12.2% at long-term follow-up (18). In the present report, the rate of trigeminal nerve toxicity was 8%, consisting only of mild dysesthesia of the trigeminal nerve.

One of the main goals in the management of AN is the preservation of hearing function after treatment. For microsurgery, hearing preservation strictly depends on the size of the tumor, the choice of the surgical approach, and, last, the experience of the surgeon (9, 29–35, 38, 61). The results of hearing preservation obtained by SRS are generally comparable with those after microsurgery. Karpinos et al. reported on serviceable hearing preservation rates of 44% and 40% for radiosurgery and microsurgery, respectively (18). Patients treated with a middle fossa and suboccipital microsurgical approach in their study presented with hearing preservation rates of 25% for small and 0% for larger tumors. Pollack et al. found a significantly higher serviceable hearing preservation rate in patients treated with radiosurgery than in patients treated with microsurgery (61). This is supported by a number of studies reporting on serviceable hearing preservation rates of 26–65% at 1–10 years follow-up (45, 49, 62–65). In the present study, hearing preservation in patients with useful or serviceable hearing before RT was 55% at 9 years after SRS. We could not find a significance in hearing preservation with regard to size of the tumors or presence of NF-2. A possible explanation is that the doses were prescribed taking into account the size of the AN, which might mask the possible effect of the RT volume on toxicity. However, although hearing preservation is comparable with or better than results obtained by microsurgery, fractionated precision RT provides a radiobiologic advantage of fractionation to further improve hearing preservation. Patients treated with FSRT at our institution showed serviceable hearing preservation rate of 94% after 5 years (57). In a study published by Meijer et al., hearing preservation after FSRT was 64% at 5 years, and Flickinger et al. found a hearing preservation rate of 78.6 ± 5.1% at 6 years (52, 64).

In conclusion, radiosurgical treatment of AN is a feasible and effective treatment alternative to microsurgery and FSRT. It is associated with a low rate of immediate and long-term toxicity by means of facial and trigeminal neuropathy as compared with microsurgery. Hearing preservation rates and local control rates are comparable with those achieved by microsurgery. However, with FSRT, cranial nerve toxicity can be further reduced. Obvious benefits of SRS are the noninvasive approach and the application of the therapeutic dose in a single fraction. Although, as a radiotherapeutic alternative to microsurgery, FSRT is the recommended treatment of choice in our institution, SRS is reserved for patients with very small AN, and for elderly patients and patients with comorbidities certainly profiting from the reduction of hospitalization and treatment times.

REFERENCES


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