Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 5, pp. 1390–1396, 2003

0360-3016/03/$–see front matter

ELSEVIER

doi:10.1016/S0360-3016(03)00444-9

CLINICAL INVESTIGATION **Brain**

SINGLE-FRACTION VS. FRACTIONATED LINAC-BASED STEREOTACTIC RADIOSURGERY FOR VESTIBULAR SCHWANNOMA: A SINGLE-INSTITUTION STUDY

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Purpose: In this single-institution trial, we investigated whether fractionated stereotactic radiation therapy is superior to single-fraction linac-based radiosurgery with respect to treatment-related toxicity and local control in patients with vestibular schwannoma.

Methods and Materials: All 129 vestibular schwannoma patients treated between 1992 and June 2000 at our linac-based radiosurgery facility were analyzed with respect to treatment schedule. Dentate patients were prospectively selected for a fractionated schedule of 5 × 4 Gy and later on 5 × 5 Gy at the 80% isodose in 1 week with a relocatable stereotactic frame. Edentate patients were prospectively selected for a nonfractionated treatment of 1 × 10 Gy and later on 1 × 12.5 Gy at 80% isodose with an invasive stereotactic frame. Both MRI and CT scans were made in all 129 patients within 1 week before treatment. All patients were followed yearly with MRI and physical examination.

Results: A fractionated schedule was given to 80 patients and a single fraction to 49 patients. Mean follow-up time was 33 months (range: 12–107 months). There was no statistically significant difference between the single-fraction group and the fractionated group with respect to mean tumor diameter (2.6 vs. 2.5 cm) or mean follow-up time (both 33 months). Only mean age (63 years vs. 49 years) was statistically significantly different ($p = 0.001$). Outcome differences between the single-fraction treatment group and the fractionated treatment group with respect to 5-year local control probability (100% vs. 94%), 5-year facial nerve preservation probability (93% vs. 97%), and 5-year hearing preservation probability (75% vs. 61%) were not statistically significant. The difference in 5-year trigeminal nerve preservation (92% vs. 98%) reached statistical significance ($p = 0.048$).

Conclusion: Linac-based single-fraction radiosurgery seems to be as good as linac-based fractionated stereotactic radiation therapy in vestibular schwannoma patients, except for a small difference in trigeminal nerve preservation rate in favor of a fractionated schedule.

Linac radiosurgery, Fractionated stereotactic radiotherapy, Vestibular schwannoma, Skull base tumors, Hearing loss.

INTRODUCTION

The traditional treatment of vestibular schwannoma is surgery, giving excellent local control rates (1–3).

Gamma knife stereotactic radiosurgery was introduced by Leksell in 1969 as a nonsurgical treatment option for vestibular schwannoma (4). From the beginning of the 1990s, a number of reports have been published on this single-fraction radiation treatment, finding local control rates similar to those with surgery, but without the possible associated surgical complications (5–9).

With the subsequent introduction of linear accelerators (linac) especially adapted for stereotactic irradiation, linac-based stereotactic radiosurgery has become an alternative to gamma knife radiosurgery. The treatment of vestibular schwannoma with linac-based stereotactic radiosurgery has given results comparable to those with gamma knife radiosurgery with respect to local control and complications (10–14).

Because linac-based stereotactic irradiation can be given as a fractionated schedule, patients might benefit from the anticipated biologic advantage of fractionation, as is seen in conventional radiation therapy. Several fractionation schedules using stereotactic irradiation have been reported, ranging from 4 fractions in 4 consecutive days to conventionally fractionated schedules of 30 fractions in 6 weeks (9, 14–20).

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Presented at the 44th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, New Orleans, LA, October 6–10, 2002.

Received Nov 4, 2002, and in revised form Feb 7, 2003. Accepted for publication Feb 19, 2003.

To date, however, no studies have been published comparing the outcomes of fractionated stereotactic radiation therapy with the outcomes of linac-based single-fraction radiosurgery in matching vestibular schwannoma patient groups.

In this report, we compare the results of a fractionated stereotactic treatment with a single-fraction stereotactic treatment to see whether one is superior with respect to local tumor control and treatment-related toxicity in patients with vestibular schwannoma.

METHODS AND MATERIALS

In 1991, the first radiosurgery facility in the Netherlands was opened at the VU University Medical Center in Amsterdam. To date, about 600 patients have been treated in this linac-based facility for various indications, such as cerebral arteriovenous malformations, brain metastases, and vestibular schwannomas. In this paper, we analyze the vestibular schwannoma treatment.

Patients

All vestibular schwannoma patients treated were included. The first patient was treated in 1992, and all consecutive patients treated at this facility until July 2000 were included in this analysis. Vestibular schwannoma was diagnosed if a patient reported unilateral sensory hearing loss and revealed the typical radiologic appearance of a cerebellopontine angle tumor on MRI.

Patients were selected for treatment if there was documented tumor progression on MRI, progression of symptoms, or both, and if largest tumor diameter was smaller than 4.0 cm. All patients who fitted these criteria were treated.

All patients were seen at the outpatient clinic by a radiation oncologist and a neurosurgeon. Before treatment, all patients were evaluated in a standardized fashion. Evaluation included an interview and a neurologic examination that focused on cranial nerve function. Facial nerve function was assessed and scored using the House-Brackmann facial nerve grading system (21). Trigeminal nerve function was assessed by asking the patient about facial pain or a numb feeling when touching the face. Hearing assessment was done in all patients before treatment by scoring the ability to use the telephone on the affected side. If patients were not able to discriminate words or could not hear at all, they were scored as deaf.

Procedure and treatment

In all patients, gadolinium-enhanced T1-weighted mprage volume MR scans were made with a slice thickness of 1 mm and reconstruction in 3 dimensions in all patients within 1 week before treatment.

With stereotactic head frame fixed, 2-mm sliced planning CT scans of the head were made of all patients on the treatment day or within 1 week before treatment. Tumor localization and delineation were done on this contrast-enhanced planning CT scan in the patients who were treated before 1997. In the patients who were treated from 1997 on, tumors were delineated on the MRI and fused with the planning CT scan using Brainscan software (Brainlab AG).

All dentate patients were treated with a fractionated schedule of 5 fractions in 7 days. In all these patients, stereotactic localization and treatment were performed with a relocatable stereotactic Gill-Thomas-Cosman head frame (Radionics Inc.) that fixes to the head by an occipital and dental impression (22). Before each treatment fraction, the relocatable stereotactic Gill-Thomas-Cosman frame was fixed to the patient's skull, and verification of the frame position was done using a depth helmet (Radionics Inc.).

Because we were not able to meet our standard of accuracy of ± 1 mm in positioning the relocatable frame in edentate patients, all edentate patients were localized and treated with an invasive stereotactic Brown-Robert-Wells head frame that fixes to the head by means of skull screws. Consequently, all edentate patients were treated with a single fraction.

In this way, two treatment groups were created: the dentate patients, who received a fractionated treatment, and the edentate patients, who received a single-fraction treatment. In the dentate patients, a total dose of 2000 cGy was given (5×400 cGy) in patients treated through 1995; in patients treated from January 1995 onward, a total dose of 2500 cGy was given (5×500 cGy). In the edentate patients, a dose of 1×1000 cGy was given in patients treated through 1995; in patients treated from January 1995 onward, a dose of 1×1250 cGy was given.

Treatments were given with a 6-MV linear accelerator (Clinac 600C, Varian Medical Systems, Inc.) that was especially adapted for radiosurgery. All treatments were planned with a single isocenter. All patients were treated with 5 noncoplanar arcs of 140° each and identical beam weighting for all arcs. Each treatment was planned with a single round collimator giving a typical spheroid dose distribution. The dose was normalized to 100% and prescribed to the 80% isodose line encompassing the tumor with a minimum margin of 1 mm. If the tumor was in contact with the brainstem, no margin was used at that location.

Because this treatment planning procedure was used for all patients, the only treatment parameters besides dose and fractionation were position of the isocenter and collimator size.

Clinical and radiologic follow-up

All patients were followed yearly and were interviewed about new or progressive symptoms with emphasis on cranial nerve V, VII, and VIII function. If hearing patients claimed their ipsilateral hearing ability was less, this was scored as hearing loss progression, even in cases where some hearing was retained.

Neurologic examination focused on facial and trigeminal nerve function assessment. If patients increased in House-Brackmann grade or if patients had new or progressive facial numbness, this was scored as treatment-related facial

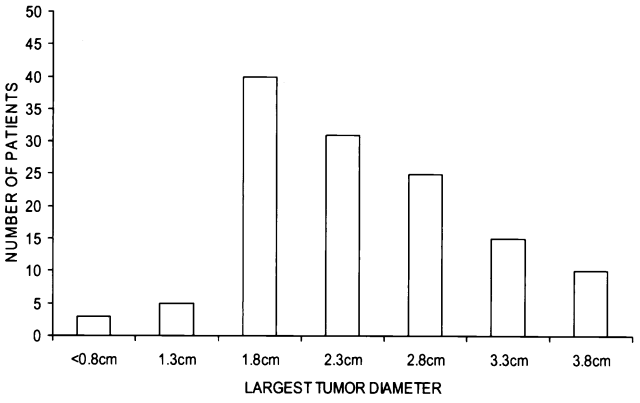

Fig. 1. Largest tumor diameters in all 129 vestibular schwannoma patients.

or trigeminal nerve function toxicity, even in cases where some function level was retained.

Tumor status in all patients was assessed yearly posttreatment by MRI. If largest tumor diameter had increased 2 mm or more compared to the previous or initial MRI, the situation was scored as tumor progression. Otherwise, the situation was scored as tumor control; a decrease in the largest tumor diameter was also scored as tumor control.

Data analysis

Tumor control probabilities and treatment-related toxicity probabilities were calculated according to the Kaplan–Meier method (23). The statistical significance of differences between actuarial curves were calculated according to the log–rank test (24). The Student's t test and Pearson's chi-square were used to determine the significance of the difference between two groups. p values of 0.05 and less were considered significant, and only two-sided results were used.

RESULTS

One hundred twenty-nine patients were treated, and all were analyzed and followed. No patient was lost to follow-up.

Patient characteristics

Before treatment, all 129 patients (100%) had hearing loss, and 57 patients (44%) were completely deaf or had no useful hearing. Eleven patients (8%) had a complete facial paralysis House-Brackmann Grade 6, and 10 patients (8%) had facial paresis House-Brackmann Grade 2–5. Various degrees of trigeminal nerve paresthesia were found in 20 patients (16%). All 129 patients (100%) had tumor progression, progression of symptoms, or both. Figure 1 shows the tumor diameters of all 129 treated patients. Mean largest tumor diameter was 2.5 cm (range: 0.8–3.8 cm), and over 90% of the tumors had a largest diameter of 1.8 cm or more. Mean age of patients was 56 years (range: 19–84 years). Previous surgery was performed in 24 patients (18%).

Treatment characteristics

Of 129 patients, all 49 edentate patients were treated with a single fraction. The first 7 were given a dose of 1×1000 cGy at 80%, and the following 42 patients received 1×1250 cGy at 80%. The remaining 80 dentate patients were given the fractionated treatment. The first 12 were given a dose of 5×400 cGy at 80%, and the following 68 patients received 5×500 cGy at 80%.

The proportion of patients (12/80) that received a low dose in the fractionated treatment group, i.e., 5×400 cGy, was not statistically significantly different from the proportion of patients (7/49) that received a low dose in the nonfractionated treatment group, i.e., 1×1000 cGy ($p = 0.9$, chi-square).

There was no statistically significant difference between the tumor diameters of the 80 patients in the fractionated treatment group (mean: 2.5 cm) and the tumor diameters of the 49 patients (mean: 2.6 cm) in the single-fraction treatment group ($p = 0.26$, t test).

Also, gender did not differ with statistical significance between the fractionated treatment group (57% male) and the single-fraction treatment group (49% male) ($p = 0.18$, chi-square).

The mean age of patients in the fractionated treatment group was 43 years, and the mean age in the single-fraction treatment group was 63 years. This difference in age was statistically significant ($p < 0.0001$, t test).

At the time of analysis, the mean follow-up time of all 129 patients was 33 months with a minimum follow-up time of 12 months and a maximum of 107 months. Follow-up time did not differ statistically significantly between the fractionated treatment group (mean: 35 months) and the single-fraction treatment group (mean: 30 months) ($p = 0.94$, t test).

Tumor control probability and fractionation

The overall actuarial 5-year tumor control probability is 96%. The actuarial 5-year tumor control probability in the fractionated treatment group was 94% vs. 100% in the single-fraction treatment group. There was no statistically significant difference between the actuarial tumor control probability in the fractionated treatment group and the single-fraction treatment group ($p = 0.14$, log–rank). All cases of tumor progression occurred no later than 3 years after the treatment, both in the fractionated treatment group and in the single-fraction treatment group.

Treatment-related toxicity and fractionation

Of all 129 patients, there were 118 patients at risk for treatment-related facial nerve toxicity. Overall actuarial 5-year facial nerve preservation probability was 96%. The actuarial 5-year facial nerve preservation probability in the fractionated treatment group ($n = 73$) was 97% vs. 93% in the single-fraction treatment group ($n = 45$). This difference was, however, not statistically significant ($p = 0.23$, log–rank). All cases of facial nerve toxicity occurred within the first year after treatment in both treatment groups.

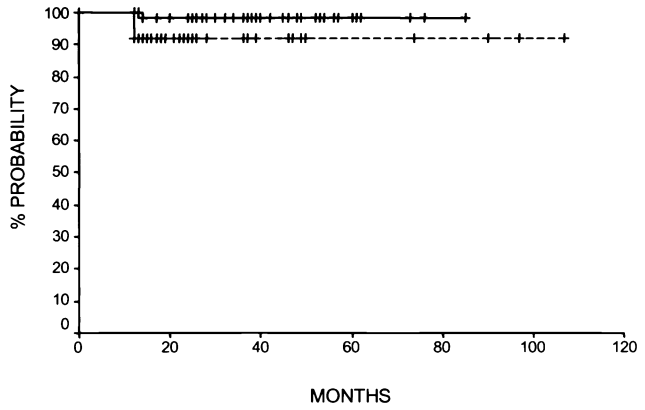

Fig. 2. Trigeminal nerve preservation probability. Dashed line is for patients in the single-fraction treatment group ($n = 49$). Solid line is for patients in the fractionated treatment group ($n = 80$).

All 129 patients were at risk for treatment-related trigeminal nerve toxicity. Trigeminal nerve preservation probability was 96% at 5 years. The 5-year trigeminal nerve toxicity probability in the fractionated treatment group was 98%; in the single-fraction treatment group, it was 92%, as shown in Fig. 2. This difference in trigeminal nerve preservation probability between the two treatment groups was statistically significant in favor of the fractionated treatment ($p = 0.048$, log–rank).

Before treatment, 57 patients were already deaf or did not have useful hearing, so consequently, only 72 patients were at risk for treatment-related hearing loss. Overall hearing preservation probability in these patients was 64% at 5 years. As shown in Fig. 3, the 5-year hearing preservation probability was 61% in the fractionated treatment group and 75% in the single-fraction treatment group. This difference, however, was not statistically significant ($p = 0.42$, log–rank).

Treatment outcome and tumor size

Mean and median tumor diameter in all patients was 2.5 cm. In the patients with tumors smaller than 2.5 cm, treatment-related trigeminal nerve toxicity (2% at 5 years) was not statistically significantly different from treatment-related trigeminal nerve toxicity (6% at 5 years) in the patients with larger tumors ($p = 0.24$, log–rank).

Also, treatment-related facial nerve toxicity (2% at 5 years) was not statistically significantly different in the patients with tumors smaller than 2.5 cm as compared to treatment-related facial nerve toxicity (6% at 5 years) in the patients with larger tumors ($p = 0.21$, log–rank).

With respect to treatment-related hearing loss, there also was no statistically significant difference between the patients with tumors smaller than 2.5 cm (30% at 5 years) and the patients with larger tumors (45% at 5 years) ($p = 0.46$, log–rank).

Tumor control probability in the patients with tumors smaller than 2.5 cm was 96% at 5 years. This also was not statistically significantly different from tumor control probability in the patients with larger tumors, which was 94% at 5 years ($p = 0.42$, log–rank).

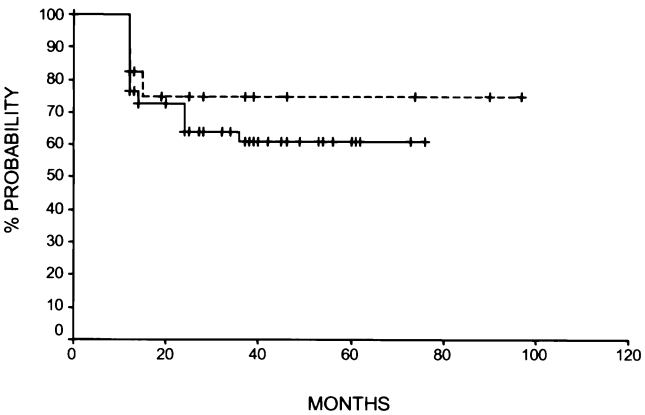

Fig. 3. Hearing preservation probability. Dashed line is for patients in the single-fraction treatment group ($n = 17$). Solid line is for patients in the fractionated treatment group ($n = 55$).

Treatment outcome and dose level

Of all the 129 treated patients, the first 19 patients received a lower dose of 5×4 Gy in the fractionation group ($n = 12$) or 1×10 Gy in the single-fraction group ($n = 7$). The remaining 110 patients who received the high dose of 5×5 Gy ($n = 68$) or 1×12.5 Gy ($n = 42$) were the subject of a separate analysis. Also, in these patients the difference between the fractionation group and the single-fraction group was not significant with respect to local control (97% resp. 100%, $p = 0.27$, log–rank), with respect to hearing preservation (58% resp. 69%, $p = 0.56$, log–rank), and with respect to facial nerve function preservation (97% resp. 91%, $p = 0.22$, log–rank). Also only the small difference in trigeminal nerve function preservation was significant (98% resp. 90%, $p = 0.047$, log–rank).

Noncranial nerve toxicity

With respect to treatment-related noncranial nerve toxicity, there were 2 patients with new symptoms possibly related to the treatment. One patient developed gait problems 6 months postirradiation with no reaction on steroid treatment. MRI revealed a large lesion in the cerebellopontine angle region on T2-weighted images, reflecting radiation damage. One other patient was given radiosurgery 9 months postoperatively for progressive residual disease. Hydrocephalus developed 4 months postirradiation, and reoperation had to be done at that time. This was the only patient who had an operation postradiosurgery.

DISCUSSION

In the past decade, stereotactic irradiation has become an important treatment option for vestibular schwannoma patients, next to watchful waiting and surgery. There is, however, still controversy about the way the radiation treatment is best given. Stereotactic irradiation of vestibular schwannoma has been applied in fractionated or in nonfractionated

schedules. A number of linac series and all gamma knife series report on the single-fraction radiation treatment of vestibular schwannoma (5–13, 25, 26). Tumor control rates in these series are all well above 90%. Tumor control rates reported in linac series, where the stereotactic irradiation has been given fractionated, are also well above 90%, irrespective of fractionation schedule (9, 15–20). There are, however, no randomized studies on a comparison of single and fractionated treatments. For a comparison, we have to rely on a comparison of published techniques. Because of differences in patient selection, tumor assessment, and treatment techniques, comparison of these series is not suitable for the detection of possible small outcome differences. In the present study, we have compared the treatment results of single and fractionated treatment in two matching patient groups. Besides a small difference in trigeminal preservation rate, we found no significant differences in outcomes between these two prospectively selected patient groups, which were similar with respect to treatment assessment and clinical and radiologic tumor characteristics.

Apart from the present single-institution study, there is only one single-institution study where a direct comparison was performed between a single fraction and a fractionated treatment. Andrews *et al.* reported on a single-institution series of 125 vestibular schwannoma patients who were irradiated either with a gamma knife single-fraction or with a linac conventionally fractionated schedule. Patient selection was based on physician preferences (9). However, the treatment groups were comparable with respect to mean follow-up time and mean tumor volume. A tumor control rate of 98% and 97%, respectively, was found for the single fraction and the fractionated treatment group. This is in agreement with the outcome of the current series of 129 patients, where we found a comparable tumor control rate and no statistically significant difference in tumor control rate between the two treatment groups.

Dose levels in both fractionated and in nonfractionated schedules mentioned in the literature seem equally effective with respect to local tumor control. We confirmed this in our current series, where there was no significant difference in tumor-related characteristics or mean follow-up time between the two treatment groups. Tumor assessment and treatment technique were also the same for both treatment groups.

Tumor diameter did not predict for tumor control probability. The tumor control rate for tumors larger than 2.5 cm was not significantly different from the tumor control rate for tumors smaller than 2.5 cm, and this is in agreement with the literature (10, 16, 19, 26). This could suggest that for smaller tumors, a lower dose might be sufficient.

Possible late treatment-related toxicity in stereotactic irradiation of vestibular schwannoma includes hearing loss. Postirradiation hearing preservation rates have been reported from 33% to 81% (7–9, 15, 17, 27). In conventional radiation therapy, the treatment is fractionated to reduce late treatment-related toxicity. This beneficial effect is also claimed in fractionated stereotactic irradiation of vestibular schwannoma with respect to hearing preservation (9, 15–20). However, comparing the results of these series with single-fraction series is hazardous, because of the differences in definitions used for hearing preservation, differences in patient selection, and differences in follow-up time. In our current series, patient selection was prospective and resulted in two treatment groups that were not significantly different with respect to the above-mentioned items. The overall hearing preservation rate in the 72 patients who were at risk for hearing loss was 64%, and there was no significant difference in hearing preservation rate between the fractionated and the single-fraction treatment group. We used a subjective hearing assessment in both treatment groups and were thus able to include all hearing patients in the analyses.

The lack of difference in late toxicity with equal tumor control rates as is seen in our current series could be explained by the fact that vestibular schwannoma cells have a very low proliferation index and thus could be considered as late-responding tissue in the linear-quadratic model (28, 29). Because the surrounding brain and nerve tissue is also late-responding tissue, one would indeed not expect an increase in the therapeutic index with fractionation, a point made also by Linskey (30).

On the other hand, Andrews *et al.* found hearing preservation in 81% of their vestibular schwannoma patients treated with fractionated stereotactic irradiation as opposed to hearing preservation in 33% of their vestibular schwannoma patients treated at the same institution with single-fraction gamma knife irradiation (9). This difference in hearing preservation rate, however, might not have been caused by the difference in fractionation schedule, but could have been caused by the higher dose inhomogeneity within the target volume in the gamma knife treatment group. The acoustic nerve passes through the target volume also; consequently, the maximum dose to the acoustic nerve would have been higher, and this could explain the higher treatment-related toxicity with respect to hearing preservation in this single-fraction treatment group.

In a very recently published study, Williams found hearing preservation in 70% of the patients treated with the same fractionation schedule of 5 fractions of 5 Gy, as opposed to hearing preservation in 100% of the patients treated with a schedule of 10 fractions of 3 Gy (31). Both groups had equal tumor control rate. In this study, however, the number of patients receiving 10 fractions was only 5, which makes an outcome comparison of the two fractionation schedules difficult. The mentioned 70% hearing preservation is slightly higher than the 64% we found in our current study. The hearing preservation rate in our current study might have been influenced by the fact that only patients with radiologic or clinical progression were treated, whereas this was not stated in the study by Williams (31).

Besides hearing loss, other possible late treatment-related toxicity in stereotactic irradiation of vestibular schwannoma includes facial and trigeminal nerve function loss. In modern series, facial nerve preservation rates have been reported

from 95% to 100% (9, 15, 17–19, 25, 27). There seems to be little or no difference in treatment-related facial nerve toxicity between the gamma knife series, with a possibly more conformal dose distribution, and the linac series and neither between fractionated and single-fraction series. The latter we could confirm in our current series, where the overall facial nerve preservation rate was 96%, and there was no significant difference between the facial nerve preservation rate in the fractionated treatment group as compared to the single-fraction treatment group. Although in our current series no special attempts have been employed to conform the dose distribution to the shape of the tumor volume, and all patients were treated with a spheroid dose distribution, we still found a very low facial nerve toxicity rate. Apparently our dose of 12.5 Gy in 1 fraction or 25 Gy in 5 fractions to the 80% isodose is below the threshold of facial nerve radiation toxicity, but on the other hand, high enough to give local tumor control.

Trigeminal nerve preservation rates in modern series have been reported from 84% to 100% (9, 15, 17–19, 25, 27). Poen *et al.* found in 16% of patients treatment-related trigeminal nerve toxicity. A linac treatment schedule was given of 21 Gy minimum tumor dose in 3 fractions in 24 h with typically multiple isocenters (15). This is a relatively high dose in a short overall treatment time compared to other modern series. All other mentioned series describe treatment-related trigeminal nerve toxicity in 0–8% of patients, both in linac and in gamma knife series and also both in single-fraction and in fractionated series. In our current series, we found a trigeminal nerve preservation probability of 98% and 92% with the fractionated schedule and with the single-fraction schedule, respectively. This difference of only 6% was, however, statistically significant in favor of the fractionated treatment schedule. It appears that, in contrast to the facial nerve, the trigeminal nerve is relatively more injured by not fractionating the radiation treatment, but only in a very small proportion of the patients.

In most reported series of stereotactic radiation treatment of vestibular schwannoma, all events, i.e., tumor progression and treatment-related toxicity, typically occur in the first 36 months after the treatment (8–12, 15–19, 26). This is what we found also in our current series, where no events were seen later than 36 months after the treatment, and no difference was seen between the fractionated and the single-fraction treatment groups in this respect.

In conclusion, we found excellent results of single-institution linac-based stereotactic irradiation in 129 vestibular schwannoma patients with respect to tumor control and treatment-related toxicity. In this series, we compared the outcomes of single-fraction treatment with fractionated treatment. Except for a small difference in trigeminal nerve preservation rate, we found no significant difference in outcomes between two prospectively selected patient groups that were similar with respect to treatment assessment as well as clinical and radiologic tumor characteristics.

Future use of dynamic arc techniques with multileaf beam shaping might further reduce the already low trigeminal nerve toxicity rate and thus eliminate the need for fractionation.

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