

FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR ACOUSTIC NEUROMAS

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Purpose: When compared with radiosurgery, fractionated stereotactic radiotherapy for acoustic neuroma (AN) offers escalation of the tumor dose and potential sparing of auditory and facial nerve functions.

Methods and Materials: Between 1996 and 2001, 249 consecutive patients have received fractionated stereotactic radiotherapy for AN. One hundred twenty-five patients had follow-up >1 year and were the subject of this report. A noninvasive, repeat-fixation mask allowed simulation by way of spiral CT. Two distinct schedules for total dose and fractionation were used. For an AN <3.0 cm in diameter (volume $1.4 \pm 0.2 \text{ cm}^3$), patients received 25 Gy given in 5 consecutive daily fractions of 5 Gy (111 patients), and for ANs $\geq 3.0 \text{ cm}$ (volume $8.1 \pm 1.2 \text{ cm}^3$), patients received 30 Gy given in 10 fractions of 3 Gy (14 patients).

Results: The percentage of decrease in tumor size was $12\% \pm 2\%$ (range 0–100%) vs. $13\% \pm 3\%$ (range 0–38%) for the 25 Gy vs. 30 Gy regimens, respectively. No patient had growth of the AN or developed facial weakness. Two patients developed transient decreases in facial sensation. The rates of hearing preservation were similar for the larger and smaller tumors.

Conclusion: Fractionated stereotactic radiotherapy may preserve normal function and control both small and large ANs. © 2002 Elsevier Science Inc.

Acoustic neuroma, Radiotherapy, Radiosurgery, Fractionated stereotactic radiotherapy.

INTRODUCTION

The roles of microsurgery vs. stereotactic radiosurgery (SRS) for the treatment of acoustic neuromas (ANs) continue to evolve (1, 2). Many regard surgery as the standard of treatment (3, 4). Although surgery offers both immediacy and low rates of recurrence, the potential loss of facial and auditory cranial nerve functions during resection remains a challenge (5). The size of the resected AN may predict the risk for loss of normal cranial nerve functions (6, 7).

SRS provides a noninvasive, single-dose treatment that results in both high rates of control and elimination of the operative morbidity for the treatment of ANs (8). For SRS, however, the risks of decreased facial and auditory functions remain a concern (9–12). Similar to surgery, the risk of loss of cranial nerve functions after SRS may be proportional to the size of the treated tumor (13). Risk is also proportional to the marginal dose (11, 14).

Fractionation is the basis for radiotherapy (RT) of many brain tumors to provide simultaneous differential sparing of normal tissues and killing of tumors (15, 16). Fractionated stereotactic RT (FSR) uses the most advantageous features of both conventional RT and SRS. When compared with RT, FSR treats the volume of irradiation more precisely (12). When compared with SRS, FSR allows fractionation

that may result in both the differential sparing of normal cranial nerves when compared with tumor (17) and the potential escalation of the total dose (18). For the AN, these factors are especially critical, because the facial and auditory nerves are immediately adjacent to, or within, the treated tumor (7). We examined FSR for both large and small ANs using two prospective schedules of fractionation. The principal end points for analysis included the initial control of tumors and preservation of the auditory and facial cranial nerve functions.

METHODS AND MATERIALS

Between 1995 and 2001, 249 consecutive patients received FSR for an AN. One hundred twenty-five consecutive patients (71 men and 54 women) had follow-up >1 year and were the subject of this report. No patients were excluded from analysis or lost to follow-up. The median clinical follow-up was 1.8 ± 0.1 years (range 1.0–5.7). The median age at the time of treatment was 54.1 ± 1.1 years (range 22.1–81.0).

Four patients underwent initial surgery for the AN and had FSR for recurrence. The intervals until recurrence were 1.2 and 6.6 years for 1 patient who had undergone two surgical procedures for the same AN; and 9.2, 9.4, and 18.4

Table 1. Patient characteristics

Patients (<i>n</i>)	125
Median age (y)	54.1 ± 1.1 (range 22.1–81.0)
Gender (<i>n</i>)	
Male	71
Female	54
Maximal transverse dimension (<i>n</i>)	
< 3 cm	111
≥ 3 cm	14
Volume (cm ³)	1.4 ± 0.2 (111) 8.1 ± 1.2 (14)
NF2 (<i>n</i>)	1
Prior surgery (<i>n</i>)	4
Median follow-up (y)	1.8 ± 0.1 (range 1.01–5.7)

Abbreviation: NF2 = neurofibromatosis type 2.

years in the remaining 3 patients. One patient was diagnosed with neurofibromatosis type 2. This patient was deaf in the contralateral ear as a consequence of surgical resection. The patient characteristics are summarized in Table 1.

Tumors were evaluated before and after treatment using gadolinium-enhanced T₁-weighted MRI (slice thickness 2–5 mm) of the AN, including the internal auditory canal. The maximal transverse dimension of the AN was recorded.

Simulation

The patient's head was supported by the rigid headrest that was attached to the base frame (BrainLab). For immobilization during simulation, the synthetic, thermoplastic mask was created and attached to the metal base frame. The Brown–Roberts–Wells localizing ring was attached to the base frame. After i.v. contrast administration, the Picker AcQSim CT provided contrast-enhanced images (2-mm slice thickness) through the entire cranium.

Treatment planning

The CT image files were transferred to the computer workstation (BrainLab) for automated external contouring, manual target contouring, and dose planning. All tumors were treated using a single isocenter. The prescription isodose was manually optimized to approximate the surface of the AN. Using the Picker AcQSim and the selection of windowing to show only bone density, the digitally reconstructed radiograph (DRR) was created to show orthogonal (AP and lateral) virtual skull radiographs. Using a transformation system that was developed in-house, the Brown–Roberts–Wells coordinates were transformed to allow display within the orthogonal, virtual skull DRR images.

Treatment

On the day of the first fractional dose, the head frame, mask, and patient's head were positioned identically to that for the simulation. Using the linear accelerator beam (Varian Clinac 18), orthogonal (AP and lateral), radiographs were taken in an orientation identical to that obtained for the

Table 2. Treatment characteristics

Treatment regimen*	Patients (<i>n</i>)	Size [†] (cm ³)	Decrease (%) after FSR
25 Gy/5 fractions	111	1.4 ± 0.2	12 ± 2
30 Gy/10 fractions	14	8.1 ± 1.2	13 ± 3

Abbreviation: FSR = fractionated stereotactic radiotherapy.

* Patients received either 25 Gy in 5 fractions or 30 Gy in 10 consecutive daily fractions.

† Dimension of treated acoustic neuromas.

DRR images as described above. Thus, by using a double exposure technique, the comparison of the AP and lateral DRR images with the actual AP and lateral images allowed confirmation of the correct positioning before the start of treatment. This procedure was repeated before each daily fraction.

Patients received 1 fraction daily and were treated on consecutive weekdays. Prospective dose selection sought preservation of normal cranial nerve function by using greater fractionation for the larger AN. Thus, for an AN < 3.0 cm in diameter (mean volume 1.4 ± 0.2 cm³), patients received 5 consecutive daily fractions of 5 Gy (25 Gy total; 111 patients), and for an AN ≥ 3.0 cm (mean volume 8.1 ± 1.2 cm³), patients received 10 fractions of 3 Gy (30 Gy total; 14 patients). All treatments were prescribed to the 80% isodose. The dimensions of the treated tumors are shown in Table 2.

Patient follow-up

Both clinical and radiographic assessments were performed every 3 months after FSR for the first year, every 6 months for the second year, and annually thereafter. Radiographic assessment included enhanced and unenhanced cranial MRI. Maximal transverse tumor measurements from the follow-up MRI studies allowed measurement of the percentage of change in size vs. time. Audiometric testing was requested every 6 months for the first 2 years and annually thereafter. Audiometric testing measured the pure tone average, speech reception threshold, and speech discrimination. The Gardner–Robinson scale was used to classify the measured hearing (19).

Statistical analysis

Measurements of age, tumor dimensions, speech reception threshold, presentation loudness for speech discrimination, and speech discrimination are presented as the mean ± SEM. The Kaplan–Meier product-limit method was used to calculate the actuarial rates of hearing preservation.

RESULTS

The tumors responded similarly regardless of size. The percentage of decrease in size of the treated tumors was 12% ± 2% (range 0–100%; 95% confidence interval 9–15%) vs. 13% ± 3% (range 0–38; 95% confidence

Table 3. Gardner-Robinson score hearing classification before and after treatment in all patients

Pre-FSR score*	Post-FSR score [†] (n)				
	1	2	3	4	5
1 (n = 16)	5	8	2	0	1
2 (n = 20)	4	13	2	1	0
3 (n = 16)	0	3	7	5	1
4 (n = 2)	0	0	2	0	0
5 (n = 2)	0	0	1	0	1

Abbreviation: FSR = fractionated stereotactic radiotherapy.

* Gardner-Robinson score and number of patients for each score before FSR treatment.

† Gardner-Robinson score and number of patients for each score after FSR treatment.

interval 5.9–20.2%) for the 25 Gy (<3.0 cm maximal diameter) vs. 30 Gy (≥3.0 cm maximal diameter) regimens, respectively.

Before FSR, the patients had diminished ipsilateral hear-

ing. For 85 patients who had audiograms done before the FSR, the ipsilateral Gardner–Robinson scores were 1 (18 patients), 2 (26 patients), 3 (31 patients), 4 (7 patients), and 5 (3 patients). The measurements of hearing after FSR showed preservation. Fifty-six patients had audiograms done both before and after FSR. The median audiometric follow-up was 1.1 ± 0.1 years. On the basis of the results of these audiograms, the Gardner–Robinson classification for hearing (19) was unchanged in 26 of 56 patients, showed an increase (worsening of hearing) in 20 patients, and decrease (improvement in hearing) in 10 patients. These data are summarized in Table 3. The probability of retention of useful hearing (Gardner–Robinson I–II) is shown in Fig. 1. The probability for preservation of useful hearing was not different (p = 0.39) for the 5 × 5 Gy vs. the 10 × 3 Gy regimens for the smaller vs. larger tumors, respectively.

No patient developed facial weakness. For trigeminal function, 2 patients had temporary, moderate decreases in facial sensation consistent with a trigeminal effect. The distribution for both patients was the ipsilateral second and

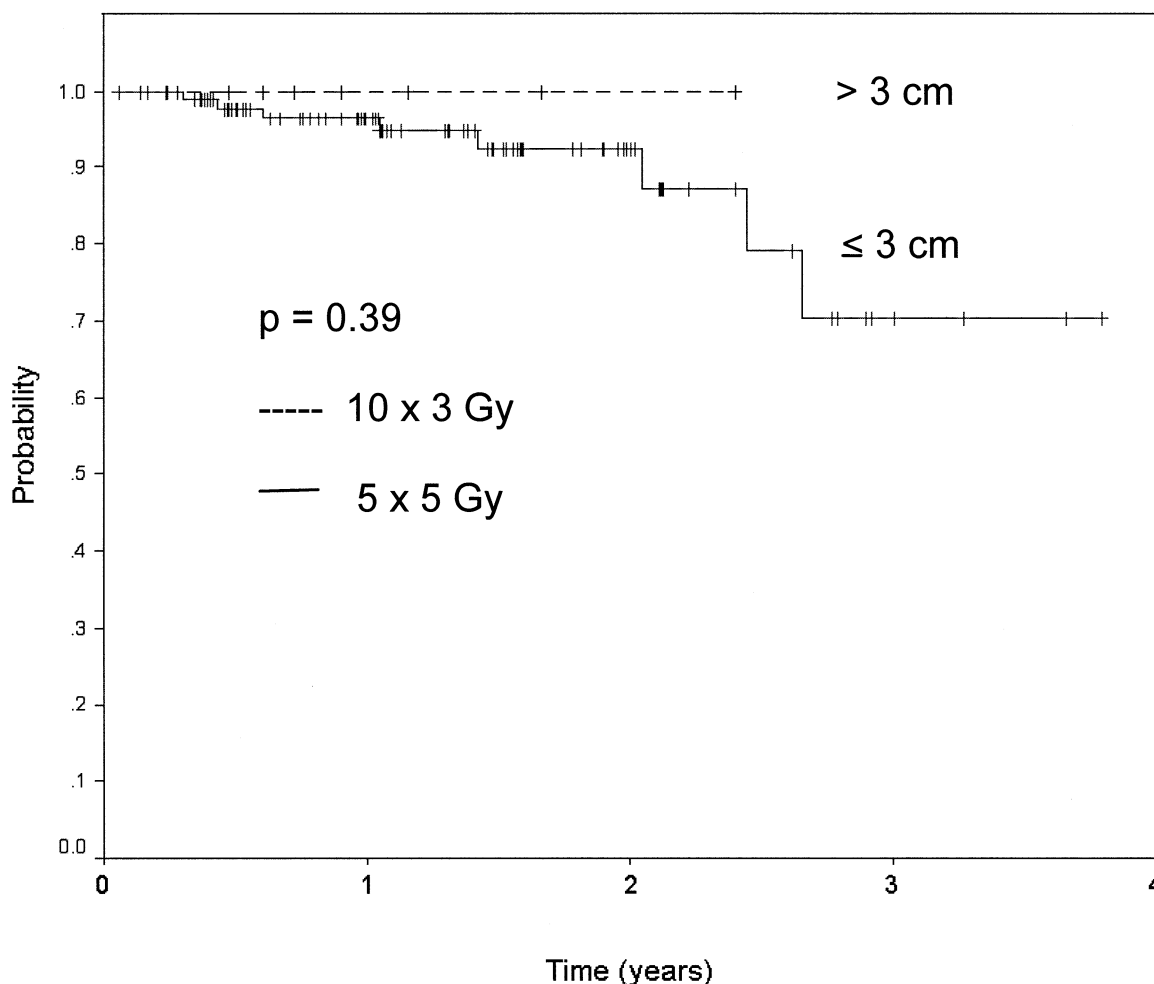


Fig. 1. Kaplan–Meier plot for probability of maintenance of serviceable hearing (Gardner–Robinson score 1 or 2) for all patients having pre- and post-FSR audiograms. Solid line represents 51 patients having ANs <3.0 cm in greatest diameter (5 fractions × 5 Gy). Dashed line represents 5 patients having ANs ≥3.0 cm (10 fractions × 3 Gy). See text for details.

third trigeminal distributions, observed 3 and 24 months after FSR. These findings resolved completely in both patients 14 and 31 months after treatment.

DISCUSSION

For both surgery and SRS, the relationships among the size of the treated AN, tumor control, and risk to normal cranial nerves have been described. For surgery, the risk of facial nerve dysfunction is proportionate to the size of the resected AN (6, 7, 20–22). Wiet *et al.* (6) noted significant increases in facial paralysis vs. the size of the resected AN in a study of 484 patients. Sampath *et al.* (7) noted that when facial nerve outcome was examined with respect to tumor size, there was clearly an increased incidence of facial nerve palsy seen in the immediate postoperative period in the case of larger tumors; 60.8% of patients with tumors <2.5 cm had normal facial nerve function, whereas only 37.5% of patients with tumors >4 cm had normal function. In a review of 58 patients and a correlation of tumor size to outcome, Are *et al.* (21) noted that the overall rate of preservation for the facial nerve was 81%, for which 20 of 21 had ANs <2 cm in size, 23 of 30 had tumors >2 cm but <4 cm in size, and 4 of 7 patients had tumors >4 cm in size. In a report of the long-term (≥ 1 year) outcome for facial nerve function in 129 patients who had surgical removal of their ANs with the aid of intraoperative neurophysiologic monitoring between 1986 and 1990, Lalwani *et al.* (22) noted that long-term facial function inversely correlated with the size of the tumor. In a prospective study with a 2-year follow-up of 35 patients undergoing AN surgery with facial nerve monitoring, tumor size was again a strong predictor of both immediate and long-term facial nerve function (23). Similarly, in a series of 276 patients with a unilateral vestibular schwannoma, Grey *et al.* (24) noted that increased tumor size was associated with worse postoperative facial nerve function. These results confirm the importance of the size of the surgically removed AN in the prediction of facial dysfunction.

For hearing preservation, the size of the resected tumor correlates so well with the outcome that candidates for postoperative preservation of hearing are selected according to the preoperative size of the AN (25). In a study of hearing preservation using tumor size as the clinical prognosticator in 60 consecutive patients, Hecht *et al.* (26) noted that removal of a tumor of <1.5 cm in size had a 50% chance of hearing preservation. In the group of patients with tumors <1.5 cm, the chance of preservation was only 16% (26). Several other studies have confirmed the relationship of size to postoperative preservation of hearing (27–30).

For cranial nerve preservation after SRS, the risks to facial, trigeminal, and auditory functions may be proportional to the size of the treated AN as well (13). In that study, the risks of both trigeminal and facial neuropathy after SRS were proportional to the irradiated length of the facial and trigeminal nerves. Similarly, Mendenhall *et al.* (31) noted complications, including facial and/or trigeminal

cranial nerves, in 13 patients (23%) after SRS. The risk of cranial nerve dysfunction was proportional to the treatment volume. Complications occurred in 3 (13%) of 23 patients who received 12.5 Gy to all volumes; 2 (9%) of 23 patients after 15–17.5 Gy to tumors of ≤ 5.5 cm³; 5 (71%) of 7 patients after 15–17.5 Gy to tumors >5.5 cm³; and 3 (100%) of 3 patients after 20–22.5 Gy to all volumes. To reduce toxicity, the doses for SRS have been reduced. Facial neuropathy decreased from 38% to 8% in one study of dose reduction, but treatment failure rose to 4% (32). In a second study of dose reduction to 13 Gy, the rate of facial neuropathy decreased to only 1%, but tumor control decreased to 91% (14). For hearing loss after SRS, the initial long-term results showed a 49% rate of decreased hearing using doses of approximately 16 Gy (10). Studies of dose reduction showed higher rates of preservation of speech discrimination after reduction of the dose to approximately 13 Gy (14). The rate of hearing preservation (same or better Gardner-Robertson class) improved from 51% to 71% after dose reduction (14). The authors observed that longer follow-up may be required to know the eventual rates of tumor control after these reductions in dose (14).

The described results of the FSR show that cranial nerve functions may be preserved regardless of the size of the treated AN. Longer follow-up is needed to assess the durability of this observation. The prospective schedules for fractionation vs. tumor size were associated with tumor control and preservation of facial and auditory functions during the follow-up interval. It is unknown whether one schedule (25 Gy in 5 fractions or 30 Gy in 10 fractions) would have resulted in the same percentage of decrease in size and preservation of function. However, the increase in fractionation (larger number of smaller fractions) vs. size is reasonable (15, 16). For larger tumors, both the volume of normal tissue immediately adjacent to the tumor and the length of normal cranial nerves within or immediately adjacent to the tumor are larger. The risk of injury after single treatment (SRS) increases exponentially with the tumor volume (33). Therapeutic gain is defined as the ratio of the tumor biologically effective dose (BED) (34) for fractionated vs. single treatment regimens. The therapeutic gain for fractionated treatment increases with the number of fractions (35). Fractionation may result in sparing of the increased lengths of normal cranial nerves that reside within or adjacent to the treated AN.

When a fractionated regimen is used, the total dose must be larger than that given in a single fraction to achieve the same magnitude of tumor cell killing and hence the same probability of tumor control. If the total dose delivered in a fractionated regimen is determined such that the tumor cell kill is equivalent to that with a given single dose, the normal tissue cell kill will be reduced (17). The α/β ratio is a radiobiologic parameter that represents the ratio of single-hit killing (α) to killing with double-hit kinetics (β) (34). For comparison with the decreased dosage regimen used recently in SRS for AN and assuming an α/β ratio of 2.5 for the tumor (14), the regimen of 25 Gy in 5 fractions has a

similar BED (75 Gy) compared with the single dose of 13 Gy (BED 80.6 Gy) (34). For α/β ratios for normal tissue (e.g., facial or auditory nerves) that are less than the α/β ratio for the tumor, FSR will result in a diminished BED for normal tissues compared with the single-dose regimen. For normal neural tissue, this may in turn result in increased preservation for any given level of tumor killing.

These results suggest that for both large and small ANs, the described schedules for FSR may result in both control of the tumor and preservation of the normal cranial nerve functions. Longer follow-up, however, is required to determine the durability of both tumor control and preservation of normal cranial nerve function beyond the studied intervals.

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