

STEREOTACTIC RADIOSURGERY AND FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR THE TREATMENT OF ACOUSTIC SCHWANNOMAS: COMPARATIVE OBSERVATIONS OF 125 PATIENTS TREATED AT ONE INSTITUTION

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Background: Stereotactic radiosurgery (SRS) and, more recently, fractionated stereotactic radiotherapy (SRT) have been recognized as noninvasive alternatives to surgery for the treatment of acoustic schwannomas. We review our experience of acoustic tumor treatments at one institution using a gamma knife for SRS and the first commercial world installation of a dedicated linac for SRT.

Methods: Patients were treated with SRS on the gamma knife or SRT on the linac from October 1994 through August 2000. Gamma knife technique involved a fixed-frame multiple shot/high conformality single treatment, whereas linac technique involved daily conventional fraction treatments involving a relocatable frame, fewer isocenters, and high conformality established by noncoplanar arc beam shaping and differential beam weighting.

Results: Sixty-nine patients were treated on the gamma knife, and 56 patients were treated on the linac, with 1 NF-2 patient common to both units. Three patients were lost to follow-up, and in the remaining 122 patients, mean follow-up was 119 ± 67 weeks for SRS patients and 115 ± 96 weeks for SRT patients. Tumor control rates were high ($\geq 97\%$) for sporadic tumors in both groups but lower for NF-2 tumors in the SRT group. Cranial nerve morbidities were comparably low in both groups, with the exception of functional hearing preservation, which was 2.5-fold higher in patients who received conventional fraction SRT.

Conclusion: SRS and SRT represent comparable noninvasive treatments for acoustic schwannomas in both sporadic and NF-2 patient groups. At 1-year follow-up, a significantly higher rate of serviceable hearing preservation was achieved in SRT sporadic tumor patients and may therefore be preferable to alternatives including surgery, SRS, or possibly observation in patients with serviceable hearing. © 2001 Elsevier Science Inc.

Acoustic schwannoma, Acoustic neurinoma, Stereotactic radiosurgery, Fractionated stereotactic radiotherapy.

INTRODUCTION

Over the past 6 years, there has been rapid progress in the application of stereotactic radiosurgery (SRS) to the treatment of acoustic schwannomas. Recent publications have reviewed a broad experience in patients with 5–10-year follow-up. Tumor control rates are $\geq 95\%$, and treatment-related morbidities have diminished with refined techniques and have remained significantly less than microneurosurgical treatments reflected in large, modern surgical series.

Radiobiologic models ascribe a direct relationship between late normal tissue damage and dose per treatment delivered to these tissues (1–4), so recent published series from a growing number of institutions, including our own,

have explored the use of either gamma knife stereotactic radiotherapy (SRT) (5) or linac-based SRT (6–14) for the treatment of benign tumors such as acoustic tumors. Although this experience is smaller and more recent, SRT data reflect comparable tumor control rates and high rates of cranial nerve preservation (6, 7, 12, 14).

Because our stereotactic radiosurgery program includes both a gamma knife (U-model) and a linac designed for and dedicated to SRS and SRT (Varian 600SR), we sought to compare these different techniques for the treatment of acoustic tumors. We originally designed a prospective randomized protocol to compare SRS and SRT paradigms, but because of either patient expectation or physician bias, we

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found accrual difficult and thereafter prospectively assigned treatments, based on uniform treatment policies, on either unit. The linac was operational 20 months before the gamma knife, and we also included 11 acoustic tumor patients who were treated before prospective enrollment for this analysis. We herein describe our experience using both techniques, specifically comparing a uniform SRS technique with a conventional fraction SRT technique and draw conclusions based on this unique comparison.

PATIENTS AND METHODS

Patient enrollment

Before treatment, all patients were discussed at a multidisciplinary tumor board and found to be suitable for either SRS or SRT. Before the gamma knife was operational, we used the linac to treat 25 acoustic tumor patients, 11 of whom had serviceable or measurable hearing. We carried forward a policy in which patients with serviceable or measurable hearing were treated with SRT at conventional fraction sizes. Patients who had lost hearing from either surgery or acoustic tumor progression were treated with a 36 Gy/4-Gy fraction hypofractionation schedule, if the trigeminal and facial nerves were intact. This patient group did well, with high rates of cranial nerve preservation and tumor control rates and will be analyzed in a separate study. We treated patients with V, VII, or VIII neuropathies with SRS. Pre-gamma knife patients included NF-2 and sporadic tumor patients. When the gamma knife became operational, patients with or without hearing were allocated to treatments on either unit, based on strong physician preferences, except for very large tumors, which we treated with SRT (6, 7, 10), based on well-established dose-volume relationships (15). All patients met the following criteria for treatment: (1) a newly diagnosed tumor with interval growth on serial MRI scans (See Fig. 1); (2) serviceable hearing on the involved side (16) without regard for growth documentation; (3) a postoperative residual or recurrent acoustic tumor; or (4) refusal of or medical contraindications to surgery. The current analysis is limited to patients enrolled for treatment with gamma knife SRS or linac-based conventional fraction size SRT.

SRS technique

Our gamma knife U-model became operational in June 1996, and treatment planning included the Leksell Gamma Plan software. Gamma knife technique involved application of the Leksell stereotactic head frame with frame shift to center the lesion as much as possible in stereotactic space. We used an MRI-based data set with a rapid acquisition gradient echo sequence and gadolinium enhancement. We qualified our MRI unit (1.5 T Siemens Magnetom) with a preclinical phantom study that confirmed spatial fidelity of this unit (17). Almost invariably, we designed a treatment plan that included a 12-Gy prescription to the 50% isodose line with multiple shot/high conformality treatments according to previously published procedures (18, 19).

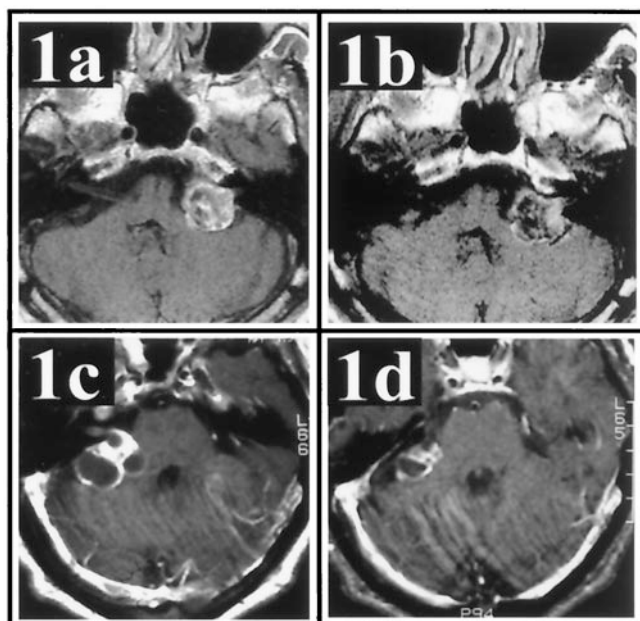


Fig. 1. Pretreatment surveillance scans in patients with moderate to severe sensorineural (< Gardner-Robertson Grade 3) hearing loss and no other associated symptoms. (a) MRI scan of Patient 83 with left acoustic tumor, who was followed from this point; (b) follow-up MRI scan of Patient 83 6 months later reveals radiographic progression. This patient was subsequently treated with SRT. (c) MRI scan of patient C.D. with right solid and cystic acoustic tumor who was followed; (d) Follow-up MRI scan of patient C.D. at 1 year follow-up reveals regression of tumor without treatment. This patient continues to be followed without treatment.

SRT technique

Our Varian 600SR dedicated linac (20) became operational in October 1994, and treatment planning included the X-Knife treatment planning software. Linac technique involved conventional 2-Gy fractions delivered daily over 5 weeks to a cumulative dose of 50 Gy. Imaging data included both CT and MRI data sets that were fused for treatment planning and treatment (21) and involved the use of the Gill-Thomas-Cosman relocatable frame (22) (Radionics) using Reprisil. Few isocenters, typically one, were used, and high conformality was established by noncoplanar arc beam shaping and differential beam weighting.

Tumor size and PIV assessment

Tumor diameters were measured and volumes calculated by one neurosurgeon (O.S.) using MRI data obtained before treatment and serial MRI scans obtained at routine intervals after treatment. Tumor volumes were assessed according to the techniques described by Linskey *et al.* (23). We also recorded pretreatment volumes generated by the treatment planning software (both X-Knife and Leksell Gamma Plan) and found comparable volumes for all but the largest tumors. We ascribed greater accuracy to initial large tumor volumes generated by the treatment planning software programs and found either volume derivation suitable for small and intermediate-size tumors. Since treatment-planning vol-

umes were unavailable after treatment, we judged tumor control rates by assessing tumor diameters over time on serial MRI scans (23, 24). Prescribed isodose volumes were generated by Leksell Gamma Plan and X-Knife. Prescribed isodose: tumor volume (PITV) was derived by dividing the prescribed isodose volume by the tumor volume.

Post-treatment clinical assessment

All patients were assessed after treatment with MRI scans and neurologic examinations that included assessment of cranial nerve function and audiometry. When assessing tumor size, apparent tumor control rates included all assessable tumors in both treatment groups, whereas actual tumor control rates included only tumors with documented growth before treatment. Trigeminal nerve function was assessed by the patient's perception of pain and a corneal reflex, and facial nerve function was assessed using the House-Brackman grading scale (25).

Patients with intact, serviceable, or measurable hearing were assessed by serial audiometry using the Gardner-Robertson grading scale (16). Pure tone average was calculated from audiometric masked bone conduction responses at 500 Hz, 1000 Hz, and 2000 Hz, and a speech discrimination score was recorded to establish a pre- and post-treatment audiometric grade. When assessing post-treatment hearing at follow-up, audiograms were scored as censored observations if hearing was maintained in the same Gardner-Robertson level for all patients with measurable hearing or remained serviceable in a subanalysis of patients with sporadic tumors only. In the former case, uncensored events were recorded for a drop in Gardner-Robertson grade, and in the latter case, uncensored events were recorded for deterioration of hearing below a Gardner-Robertson 2 level. If post-treatment audiograms exceeded a 1-year interval with an associated drop in Gardner-Robertson hearing grade from 1 or 2 to 3 or lower, the halfway point was chosen as the time of the uncensored event. Raw hearing preservation rates were calculated as the number of patients maintaining one Gardner-Robertson grade before and after treatment divided by all patients with measurable hearing at the same pretreatment grade. Serviceable hearing preservation rates were calculated as the number of patients maintaining either Gardner-Robertson Grade 1 or 2 in the post-treatment period divided by all patients with Gardner-Robertson Grade 1 or 2 hearing at pretreatment. In all cases, actuarial hearing preservation rates were established by the Kaplan-Meier product limit method.

Statistical analysis

All patient data were entered into a statistical spreadsheet (Statview 5.01), and statistical analyses were performed using this software, with mean values reported \pm standard deviation and statistical significance established at $p < 0.05$. Tumor control and cranial nerve preservation rates were established using the Kaplan-Meier product limit method, and differences were assessed by the log-rank test with statistical significance established at $p < 0.05$.

Table 1.

Patient characteristics	Unit*	
	SRS	SRT
<i>n</i> (tumor/patients)	69	56
Mean age	61	57
Gender (M/F)	33/36	24/32
Mean follow-up (weeks)	119 \pm 67	115 \pm 96
Previous surgery	17	7
Mean tumor volume (cc)	2.92 \pm 2.6	2.78 \pm 2.4
Intracanalicular (<i>n</i>)	11	10
<1 cc	9	8
1-2.99	21	17
3-5.99	19	8
6-10	8	9
>10	1	4
No. of isocenters	5.1 \pm 3.4	1.2 \pm 1 [‡]
PITV [†] ratio	1.81 \pm .73	2.7 \pm 1.8 [§]
Dose prescription (isodose line %)	50 \pm 2.8	86.2 \pm 8
Tumor type (sporadic vs. NF-2)	64/5	46/10

* One NF-2 patient was treated on both units.

[†] PITV is the ratio of prescribed isodose volume to tumor volume.

[‡] $p < 0.0001$ vs. gamma knife.

[§] $p < 0.0005$ vs. gamma knife.

^{||} $p < 0.0001$ vs. gamma knife.

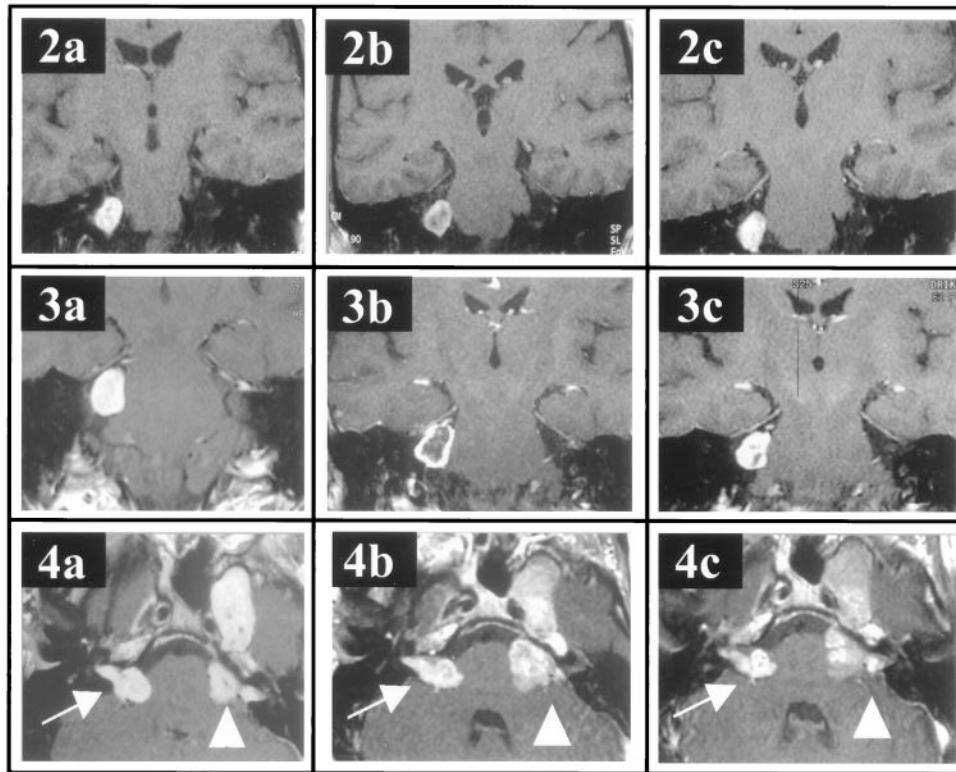
RESULTS

Patient characteristics

One hundred twenty-five patients with acoustic tumors were treated, as summarized in Table 1. Mean ages were similar, as were tumor sizes and gender distribution. Sixty-nine patients were treated on the gamma knife and 56 patients on the linac, with 1 NF-2 patient common to both units. This patient had one tumor treated with SRS and the contralateral tumor with SRT. An additional NF-2 patient had only one tumor treated with SRT; this treatment failed, and the patient was subsequently treated with SRS on the gamma knife. Although this tumor was scored in the SRT group, it was not included in the SRS group, because the cumulative tumor dose was not comparable to that of the SRS cohort. Six unilateral serviceable hearing NF-2 patients had both tumors treated with SRT on the linac, the first two of whom were treated before the gamma knife was operational, and the sixth of whom is under treatment. In the sixth case, hearing was serviceable in both ears, and as of this analysis, the right side has been treated, and the left side is under treatment with SRT. Two patients in the SRS group died, one from unrelated causes and one from complications related to NF-2. One patient in the SRT group moved out of the region and was lost to follow-up. The number of isocenters, dose prescription isosurfaces, and PITV ratios were significantly different when both groups were compared (Table 1).

Radiographic treatment response

Both SRS and SRT treatment groups and both tumor types manifested a similar response to treatment, as featured



Figs. 2–4. Serial MRI scans of representative patients from each treatment group. **2a–4a:** MRI scans of Patients 1, 62, and 53 respectively, at treatment; **2b–4b:** MRI scans of same patients, respectively, at 6 month follow-up with loss of central enhancement; **2c–4c:** MRI scans of same patients, respectively, at one year with tumor shrinkage and return of gadolinium contrast-enhancement; **2a–c:** Patient 1 was treated with Gamma Knife SRS utilizing a 5 isocenter/12 Gy dose prescription to the 50% isodose line; **3a–c:** Patient 62 had Gardner-Robertson Grade I hearing and was treated without further observation with LINAC SRT utilizing a 1 isocenter/2 Gy daily dose prescription to the 82% isodose line for a cumulative dose of 50 Gy with preservation of hearing at a Gardner-Robertson Grade I level at 173 weeks follow-up; **4a–c:** Patient 53, diagnosed with NF-2, has bilateral acoustic tumors as well as a trigeminal schwannoma invading Meckels cave on the left. The right acoustic tumor (arrow), associated with Gardner-Robertson Grade I hearing, was treated first with LINAC SRT utilizing 1 isocenter/2 Gy daily dose prescription to the 93% isodose line for a cumulative dose of 50 Gy. Six months later, the left acoustic and trigeminal schwannomas (arrowhead) were simultaneously treated utilizing a 3 isocenter/4 Gy twice weekly dose prescription to the 85% isodose line for a cumulative dose of 36 Gy. Hearing in the right ear remains a Gardner-Robertson Grade I level at 254 weeks follow-up.

in Figs. 2–4. In most cases, a biphasic MRI radiographic response was noted that included a loss of central enhancement, sometimes with a corresponding mild increase in tumor volume that was generally observed by 6 months after treatment. Later MRI images revealed a decrease in tumor size with an associated return of gadolinium contrast enhancement. We as others assume that, in the post-treatment period, loss of enhancement reflects necrosis, and subsequent shrinkage with enhancement represents scar formation.

Tumor control rates

Because patients with measurable hearing were not followed with serial MRI scans to document tumor growth, an apparent high tumor control rate was noted for sporadic tumors in both groups for all patients in this analysis. Of patients with a follow-up of ≥ 6 months, we noted control rates of 98% and 97% for the SRS ($n = 63$) and SRT ($n = 46$) groups, respectively (Fig. 5). When the measurable

hearing group was excluded, similar actual tumor control rates of 98% ($n = 56$) and 100% ($n = 22$) for SRS and both SRT groups, respectively, were noted (data not shown). More discrepant tumor control rates were noted in NF-2 patients, with an 80% control rate in the SRS group ($n = 5$) compared with a 67% control rate in the SRT group ($n = 10$), not statistically significant at $p = 0.6615$.

Incidence of treatment-related trigeminal neuropathy

Sixty-four of 69 SRS patients and 50 of 56 SRT patients had intact trigeminal nerve function before therapy for all patients in this analysis. In the post-treatment period, the incidence of treatment-related trigeminal neuropathy was low in both groups, with preservation rates of 95% for the SRS group and 93% for the SRT group (Fig. 6). Three patients in the SRS group and 5 patients in the SRT group had a pre-existing trigeminal neuropathy. After treatment, 2 patients in the SRS group and 1 patient in the SRT group

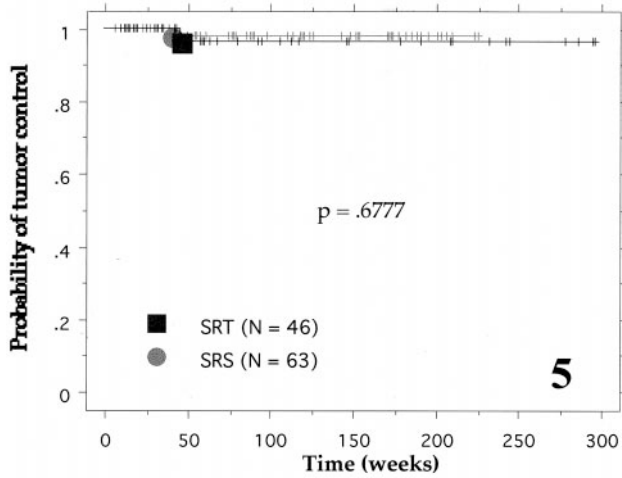


Fig. 5. Kaplan–Meier plot for probability of tumor control for all sporadic tumor patients.

noted improvement with return of partial or complete facial sensation after treatment.

Incidence of treatment-related facial neuropathy

Fifty-seven of 69 SRS patients and 50 of 56 SRT patients had intact facial nerve function before therapy. In the post-treatment period, the incidence of treatment-related facial neuropathy was low in both groups, with preservation rates of 98% for both groups (Fig. 7). One patient in each treatment group with a pre-existing facial neuropathy manifested improvement in facial nerve function after treatment.

Incidence of treatment-related hearing loss

Mean follow-up was shorter for both groups of patients with serviceable hearing at interim analysis. This was a reflection of the fact that patients were less compliant with scheduled audiograms at later follow-up intervals. Table 2 features Gardner–Robertson hearing classification before

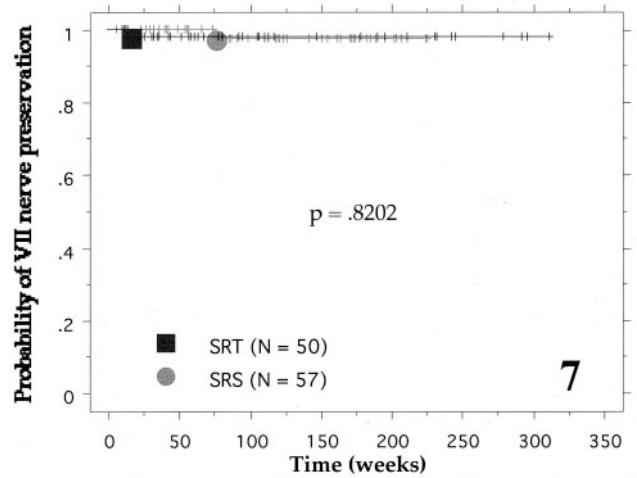


Fig. 7. Kaplan–Meier plot for probability of facial nerve preservation in all patients

and after treatment for all patients with measurable hearing in this study. Three SRT cases, one before and two during prospective accrual, were excluded from post-treatment analysis, as detailed below.

One SRT patient had serviceable hearing at the inception of SRT and in the post-treatment period, but developed a gait ataxia because of an enlarging cyst within the acoustic tumor, a complication previously described after SRS treatment (26). He elected to undergo surgical resection of the enlarging cyst, after which he lost hearing in the ipsilateral ear and, although he was scored as tumor progression, he was not scored in the post-treatment serviceable hearing subgroup (Fig. 10a–c). In another SRT case, post-treatment audiometric data were unobtainable from India, and in a third SRT case, the patient had audiometrically confirmed pretreatment moderate to severe sensorineural hearing loss, which returned to a serviceable level with steroids but fluctuated thereafter. In this case, steroids were considered an independent variable affecting hearing, and this patient was not scored in the post-treatment period.

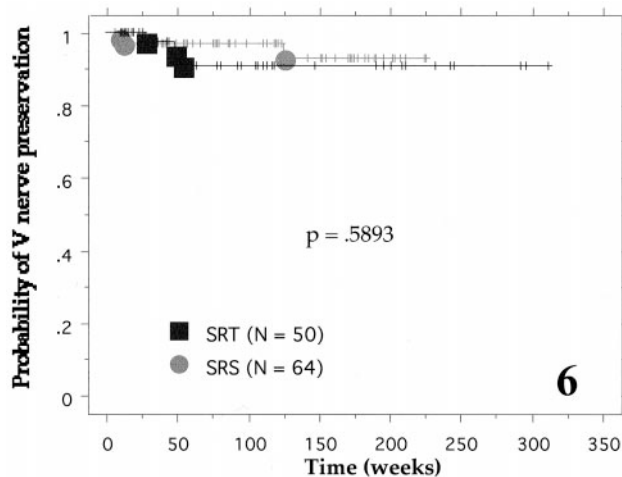


Fig. 6. Kaplan–Meier plot for probability of trigeminal nerve preservation for all patients.

Table 2. Hearing classification before and after treatment in all patients with measurable hearing at ≥6 months follow-up

Treatment mode	Gardner-Robertson grade	
	Pretreatment (n)	Post-treatment (n)
Gamma knife		
I	7	2
II	5	2
III	4	13
IV	0	0
V	1	0
Linac		
I	16/3*	8/3
II	5/3	9/2
III	6/0	11/0
IV	1/0	0/0
V	0/0	0/1

* Sporadic/NF-2.

Unlike other cranial nerve preservation rates that were comparable, we noted significantly higher hearing preservation rates in the patients treated with conventional fraction stereotactic radiotherapy. Audiometric follow-up was a mean of 82 weeks (range 6–265) and a median of 42 weeks for the SRT group ($n = 34$), and a mean of 68 weeks (range 20–151) and a median of 46 weeks for the SRS group ($n = 17$). The probability of maintaining the same Gardner–Robertson grade remained significantly higher in the SRT group ($p = .0461$), as featured in Figure 8a. All 17 of the SRS patients with measurable hearing had sporadic tumors, and the SRT group with measurable hearing included 6 NF-2 patients and 28 patients with sporadic tumors.

Analyzing only sporadic tumor cases with serviceable hearing, the probability of maintaining serviceable hearing remained significantly higher at 81% in the SRT group v. 33% for the SRS group ($p = .0228$), as featured in Fig. 8b. Follow-up was a mean of 64 weeks (range 17–190) and a median of 38 weeks for the SRT group ($n = 21$), and a mean of 57 weeks (range 24–151) and a median of 41 weeks for the SRS group ($n = 12$). One SRT patient lost hearing at 162 weeks, with radiographic evidence of tumor shrinkage but marked cystic degeneration within the residual tumor volume. Pre- and post-treatment audiometric data for sporadic tumor patients are summarized in Table 3. Our pre-treatment audiometric data in both SRS and SRT groups, including the SRT intracanalicular (i.c.) subgroup, are very similar to data for i.c. acoustic tumors recently reported by Niranjani *et al.* (27), as featured in Table 3. In a comparison, both treatment modalities manifested a significant intra-group decline in hearing function, quantified as an increase in post-treatment pure tone averages and decrease in speech discrimination scores when compared to pre-treatment values by paired t test. The SRT hearing group in the current series, however, maintained a significantly lower pure tone average in the post-treatment period when compared by unpaired t test to the SRS group reported by Niranjani *et al.* ($p = .0120$). Mean speech discrimination scores also remained significantly higher in the SRT when compared to the SRS group ($p = .0466$).

We also assessed hearing preservation as it might relate to pre-treatment Gardner–Robertson (G-R) grade. Patients with G-R grade I hearing had a significantly higher probability of preserving functional hearing than did G-R II patients (Fig. 8c). When differentiated by treatment group, SRT patients with pre-treatment G-R I grade hearing had a significantly greater probability of maintaining serviceable hearing than did SRS patients with pre-treatment G-R I hearing (Fig. 8d). Post-treatment audiometric PTA and SDS data were uniformly better in the SRT group when compared to the SRS group, but not statistically significant (data not shown). This was particularly evident in the evaluation of PTA in the G-R grade I patients ($p = .0679$).

While no NF-2 patients in the SRS group had serviceable hearing, 4 of 6 patients in the SRT group maintained pre-treatment serviceable hearing (Fig. 8e). Pre- and post-treat-

ment audiometric data for NF-2 patients are featured in Table 3.

Noncranial nerve treatment-related morbidities and/or improvements

We have recently reported our experience with acute and subacute treatment-related noncranial nerve morbidities after SRT for a variety of intracranial lesions (28). While reassessing for acoustic tumors in the current analysis, we found in both treatment groups a similar array of noncranial nerve morbidities, which are summarized in Table 4.

Six symptoms in 6 or 10% of SRS patients and four symptoms in 7 or 13% of SRT patients experienced noncranial nerve morbidities. We noted three patients with post-treatment MRI scans featuring T2-weighted changes located either in the contiguous brainstem, cerebellum, or mesial temporal lobe (1 SRS and 2 SRT). In one case, these radiographic findings were associated with symptoms including vertigo and mild gait (Fig. 9a–c).

The most common post-treatment symptom was a complaint of gait disturbance that occurred generally within 4 to 6 months of treatment. This was often a subjective complaint without neurologic signs associated with gait disturbance, but when the disturbance was objectively found, it was associated with either a presumed vestibular dysfunction (no associated nystagmus was noted) or hydrocephalus. In 1 SRS patient, symptoms of vertigo and gait disturbance improved after placement of a shunt for hydrocephalus. In 2 SRT patients, pretreatment vertigo symptoms improved, and in a third SRT patient, a pretreatment gait disturbance improved. One symptomatic SRT patient with cystic tumor degeneration elected to undergo surgical removal with subsequent hearing loss (Fig. 10).

DISCUSSION

An extensive literature exists in neurosurgery, the otorhinolaryngology/neuro-otology subspecialty, and more recently in radiation oncology regarding the natural history and treatment of acoustic tumors (6, 7, 11, 12, 14, 18, 19, 23, 29–63). The natural history usually features both progression of tumor size and hearing loss (12, 29, 35, 44, 56, 58, 59, 64). A Danish study (59) reviewed acoustic tumor growth patterns and found no measurable growth in 18% and regression in 8%. At our institution, 520 of 617 acoustic tumors referred for treatment were operated on, and 97 were followed. Of tumors that were followed, 74% increased in size, 18% remained the same size, and 8% decreased in size (W.A. Buchheit, personal communication), reflecting the same growth rates as the above-mentioned Danish study. One recent study described no growth in 26% to 83% of patients over 1 or 2 years of follow-up (65). These studies support documentation of growth before treatment to assess accurate tumor control rates thereafter (See Fig. 1). Exceptions to this policy include large symptomatic tumors or patients with intact or serviceable hearing, issues that are discussed below.

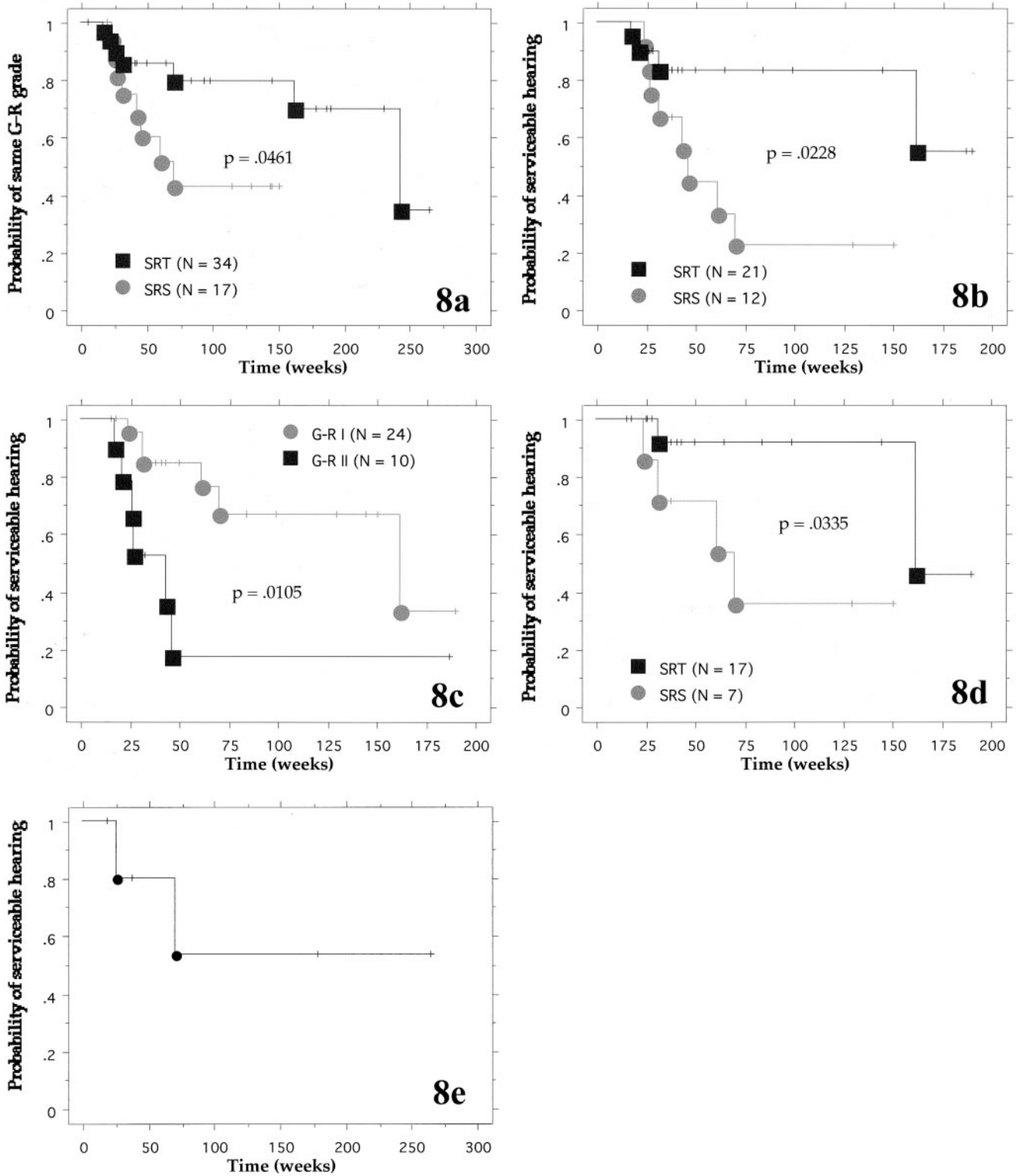


Fig. 8. (a) Kaplan–Meier plot for probability of the same Gardner–Robertson hearing grade for all patients; (b) Kaplan–Meier plot for probability of maintaining serviceable hearing grade for all patients; (c) Kaplan–Meier plot for probability of maintenance of serviceable hearing by pre-treatment G-R Grade; (d) Kaplan–Meier plot for probability of maintenance of serviceable hearing in patients with pre-treatment G-R I hearing by treatment group; (e) Kaplan–Meier plot for probability of serviceable hearing in NF-2 patients treated with SRT.

Modern microneurosurgery techniques have significantly decreased morbidity and mortality (61, 66–68), but recent literature also reflects the application and refinement of

stereotactic radiosurgery techniques (18, 19, 69) (For a recent general review, see Mehta [70]). Both treatment modalities have established a correlation between tumor size

Table 3. Pre- and post-treatment current and published audiometric data

Unit	N	Tumor vol. (cc)	Follow-up (weeks)	Pretreatment audiometric data		Post-treatment audiometric data	
				Pure tone ave.	Speech discrim.	Pure tone ave.	Speech discrim.
SRS serviceable, interim	12	1.40 ± 1.08	56 ± 42	26.3 ± 10.2	86.3 ± 13.4	46.2 ± 14.6	57.3 ± 29.4
SRT serviceable, interim	21	1.93 ± 2.66	64 ± 57	22.8 ± 11.6 [‡]	89.9 ± 11.6	33.6 ± 17*	72.9 ± 31.9
SRT serviceable subgroups*							
Intracanalicular	8	(i.c. [†])	69.4 ± 24.5	19.5 ± 9.2	90 ± 13.9	25.4 ± 14.1 [‡]	84.5 ± 21.4 [§]
NF-2	6	5.3 ± 3.3	185 ± 101	30 ± 15.9	85 ± 18.8	39.4 ± 24.7	71 ± 41.3
SRS serviceable (Niranjan <i>et al.</i> 27)	15	(i.c. [†])	133 ± 79	26.5 ± 13.9	84.9 ± 13.8	42.0 ± 19.8	63.9 ± 35.9

* $p = .0395$ v. SRS.[†] Intracanalicular.[‡] $p = .0120$ v. Niranjan.[§] $p = .0466$ v. Niranjan.

and associated treatment-related morbidity, but radiosurgery series have demonstrated markedly diminished cranial and noncranial nerve morbidities, even for larger tumors (19). When compared according to treatment-related morbidity and patient satisfaction, stereotactic radiosurgery emerges as a preferred treatment by patients; it also has a higher degree of cost-effectiveness in the United States and abroad (52, 71, 72).

Our stereotactic radiosurgery program includes both a gamma knife and a dedicated linac. Since SRS and SRT techniques differ significantly enough to raise questions of therapeutic advantage, we originally designed a prospective randomized paradigm to compare SRS and SRT paradigms, but because of either patient expectation or physician bias, we found accrual difficult. Thereafter, we performed prospective uniform treatments on both units, except for large tumors, which were treated with SRT on the linac. After an interim analysis, we assigned patients with serviceable hearing to SRT.

The higher dose conformality achieved with the gamma knife might suggest a higher rate of tumor control, and the higher dose homogeneity achieved with linac might suggest less treatment-related morbidity. Dose conformality and homogeneity remain, however, controversial issues. With gamma knife treatments, later reported incidences of cranial neuropathy dropped with the use of smaller collimators, more isocenters, and the use of MRI data to enhance target identification and thus dose conformality (18, 19). Contrasting with these observations, a more recent gamma knife study (34) found that, in addition to tumor diameter, a higher number of isocenters was significantly associated with trigeminal, facial, and vestibulocochlear nerve dys-

function after treatment. The latter observations are supported by an earlier linac study that found a significant correlation between dose inhomogeneity (number of isocenters) and the rate of cranial and noncranial neuropathies (73).

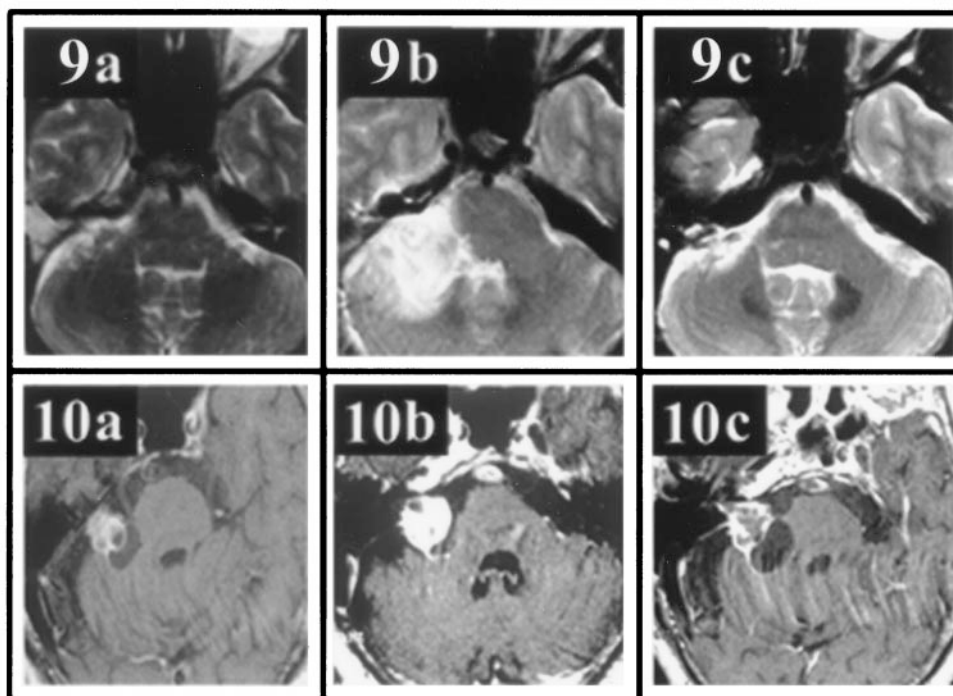
Despite these issues, the most recent radiosurgery series reveals few differences in outcomes when compared with linac-based SRT methods (6, 10, 11, 14) or even conventional radiotherapy (40). Although the safety and efficacy of all these techniques appear similar, a caveat to this comparison remains shorter SRT follow-up and an exception to treatment outcome is superior post-treatment serviceable hearing, in the SRT group discussed below. Our data corroborate SRS and SRT studies (Tables 2, 4, 6, 7 and Figs. 6–8) and additionally reveal comparable MRI radiographic responses when assessing the timing and biphasic incidence of contrast enhancement and rates of tumor shrinkage (Figs. 2–4).

Noncranial nerve morbidities observed in both groups were comparable (Table 4). In most cases, symptoms were self-limiting, but in five cases symptoms were related to hydrocephalus, requiring shunt placement in both treatment groups. We and others have previously ascribed the development of hydrocephalus to SRT (6, 7, 37, 39, 74) and feel this morbidity may share a common pathophysiologic mechanism in both the SRS and SRT groups. Hydrocephalus occurred roughly when MRI-documented tumor necrosis occurred in both groups, and perhaps proteinaceous debris may be sloughed into the perimesencephalic cistern, abnormally elevating CSF protein and causing a communicating hydrocephalus (6, 7, 39).

SRS and SRT both achieved high rates of preservation of

Table 4. Post-treatment noncranial nerve morbidities

Unit	Vertigo	Gait ataxia	Headache	Hydrocephalus	MRI transient T-2 weighted changes
Gamma	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (2.9%)	1 (1.4%)
Linac	1 (1.7%)	2 (3.6%)	2 (3.6%)	2 (3.6%)	2 (3.6%)



Figs. 9–10. MRI scans of patients with post-treatment symptoms. **9a&10a:** MRI scans of Patients 84 and 135 at treatment; **9b&10b:** MRI scans of same patients, respectively, at 6 month follow-up; **9c&10c:** MRI scans of same patients, respectively, at one year. **9a–c:** Patient 84 underwent previous surgery and was noted to have radiographic recurrence which was treated with 2 Gy fractions. At six months she noted mild gait ataxia and the MRI scan (**9b**) revealed T-2 weighted signal change in the contiguous cerebellum; symptoms were self-limiting and the subsequent MRI scan at one year (**9c**) revealed resolution of T-2 weighted penumbra. This patient was scored as a noncranial nerve treatment-related morbidity. **10a–c:** Patient 135 had a right acoustic tumor with Gardner-Robertson Grade I hearing. Without further observation he was treated with 2 Gy fractions but noted by six months a progressive gait ataxia with associated vertigo and associated tumor enlargement (**10b**). He was treated initially with Medrol dose packs with some palliation but symptoms worsened over the ensuing six months. An MRI scan at one year (**10c**) revealed shrinkage of the solid tumor component but mesial cyst enlargement. This patient subsequently underwent surgical resection with associated loss of hearing. This patient was scored as a tumor control failure.

facial and trigeminal nerve function after treatment (See Figs. 6 and 7). As in previously reported series, rates of trigeminal neuropathy occurred within 6 months in the SRS group but were delayed to 1 year in the SRT group, and both groups revealed onset of facial neuropathy by 1 year. Cranial neuropathies generally occurred later in the SRT groups, similar to results with conventional fraction radiotherapy (CF-RT) (40), suggesting that the longer SRT follow-up has provided a more valid comparison of these treatment groups.

The earlier reported frequencies of facial and trigeminal neuropathies in patients receiving radiosurgery were tumor volume-dependent (23) and wide-ranging in frequency. Noren noted only a 15% incidence of facial neuropathy and an 18% rate of trigeminal neuropathy (46), and Mendenhall *et al.* described an 18% rate of either trigeminal or facial neuropathy (41), whereas Linskey *et al.* (37) described new post-treatment facial neuropathy in 30% of cases; at the Mayo Clinic, rates of cranial neuropathy were as high as 50% and 56% for facial and trigeminal neuropathies (32). Cranial nerve morbidities have improved over the last 5 years to a 6% range currently, and this improvement has been ascribed to lower isodose prescriptions in a 12–14-Gy

range (18, 19). In a recent analysis at the Mayo Clinic, neither vestibulocochlear nerve nor facial nerve morbidity was correlated with tumor diameter but was significantly correlated with isodose prescription (43). This analysis concurred with another study in which maximum dose prescription but not tumor size was correlated with cranial nerve morbidity (75). Neither of these studies concurred with the earlier observations by Linskey *et al.* that tumor diameter was an important variable (23), or with a recent Korean study in which neither isodose prescription nor tumor volume correlated with cranial neuropathies (76). These contradictory findings leave the issue of tumor volume unresolved, but tumor volume may remain an important variable correlated with trigeminal and/or facial neuropathies only at higher tumor surface isodose prescriptions.

Dropping tumor dose too much also raises a concern, however. In one recent analysis, acoustic tumor margin doses, when dropped from 12.5 Gy to 10 Gy, were associated with a 6-fold greater incidence of tumor regrowth after SRS (77). One unresolved issue with modern SRS technique remains long-term tumor control at lower dose prescriptions, and longer follow-up will be necessary to assess

Table 5. Natural history of hearing in acoustic tumor patients

Author	<i>n</i>	Pts. with G-R I-II	Period of observation	Percent with hearing loss	Average hearing loss/yr
Thomsen and Tos (56) (1983)	19	19	4.2 years	–	9 dB
Nedzelski <i>et al.</i> (44) (1986)	6	6	5 years	–	6 dB
Kanzaki <i>et al.</i> (35) (1991)	132	–	>6 months	52% (68)	–
Charabi <i>et al.</i> (29) (1995)	123	28	20 years	75% (21)	–
Yamamoto <i>et al.</i> (64) (1998)	13	7	21 months	62%	–
Shirato <i>et al.</i> (12) (1999)	27	27	35 months	69%	–

efficacy at this dose. In the present study, further follow-up will be necessary for the 12-Gy SRS cohort and, for that matter, also for the SRT paradigms. The SRT paradigm as we have designed it promises to reproduce the same long-term control rate described by Maire *et al.* with conventional fraction radiotherapy (40).

The literature supports a natural course of progressive hearing loss, as noted in Table 5. In one study, for example, 75% of acoustic tumor patients observed lost eligibility for hearing preservation surgery because of hearing loss (29). We adopted a policy of up-front treatment in patients with serviceable hearing, with the hypothesis that focused radiation might stabilize or improve hearing while simultaneously controlling tumor growth. In the prospective randomized trial noted above, patients with radiographically documented acoustic tumors were either observed or treated with SRT (12). Patients in both groups lost hearing at comparable rates, while the SRT group reflected much higher tumor control rates, demonstrating an advantage of treatment over observation (12).

When assessing hearing preservation in either group, we noted shorter mean follow-up, which is a reflection of fewer audiograms obtained at later follow-up due to poor patient compliance. Generally, if patients had no difficulty with hearing, they did not want to go through the effort of audiometry after a certain point in follow-up. Despite this shortcoming, we noted high early rates of hearing preserved

at the pretreatment level in the SRT group (Figs. 8a–d), in agreement with other reported fractionation techniques reported in recent literature (78, 79) (Table 6). This contrasts with our results with SRS (Figs. 8a–d), which fall at the low end of a range of hearing preservation rates reported in other series (Table 6, 33–56%). Published audiometric data support this difference. A subanalysis of intracanalicular tumors reveals a significant increase in post-treatment pure tone average after SRS (27) ($n = 15$; $p = 0.0312$, paired t test) not seen after SRT in the current series, inclusive of all patients ($n = 8$; $p = 0.2268$; Table 3). This comparison suggests an advantage with SRT even for intracanalicular tumors, but our follow-up is notably half of the follow-up in this published series. Recently reported audiometric data for sporadic tumors reveal no significant losses in speech reception threshold or speech discrimination after fractionated stereotactic radiotherapy (79).

If it is assumed that the biologic response of all tissues to radiosurgery is related to dose rate (80, 81), and acknowledging that the cochlear nerve, like the optic nerve (82), has a low threshold for injury, dose rate may be related to hearing loss (83). Disparities in gamma knife hearing preservation rates may represent patient cohorts treated with cobalt sources at distinctly different mean dose rates. Our series, for example, reflects a lower hearing preservation rate than the Pittsburgh series in which higher hearing preservation rates were ascribed to better target definition with MRI from 1992 hence (18).

Table 6. Published post-treatment serviceable hearing results, sporadic tumor patients

Author	Treatment mode	Unit	Treatment imaging modality	Pretreatment serviceable hearing (<i>n</i>)	Post-treatment serviceable hearing	
					<i>n</i>	(%)
Flickinger <i>et al.</i> (18) (1996)	SRS	gamma knife	CT	45	18	40
		gamma knife	MRI	28	16	56
Thomassin <i>et al.</i> (55) (1998)	SRS	gamma knife	N/S	48	24	50
Miller <i>et al.</i> (43) (1999)	SRS	gamma knife	CT ($n = 12$) & MRI ($n = 70$)	13	5	39
Kagei <i>et al.</i> (74) (1999)	SRT	Linac	CT	15	12	78
Poen <i>et al.</i> (88) (1999)	HF-SRS	Linac	CT or MRI	13	10	77
Current series	SRS	gamma knife	MRI	12	4	33
	SRT	Linac	CT/MRI*	21	17	81

* CT and MRI data fused into one image for treatment planning (21).

Abbreviations: SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; HF-SRS = hypofractionated stereotactic radiotherapy.

Table 7. Post-treatment serviceable hearing results, NF-2 patients

Author	Treatment mode	Unit	Treatment imaging modality	Pretreatment serviceable hearing (<i>n</i>)	Post-treatment serviceable hearing	
					<i>n</i>	(%)
Glasscock <i>et al.</i> (68) (1993)	Surgery	NA	NA	29	7	24
Linskey <i>et al.</i> (85) (1992)	SRS	gamma knife	CT	5	0	0
Subach <i>et al.</i> (54) (1999)	SRS	gamma knife	MRI	9	6	67
Kida <i>et al.</i> (86) (2000)	SRS	gamma knife	NS	12	4	33
Current series	SRT	Linac	CT/MRI*	6	4	67

* CT and MRI data fused into one image for treatment planning (21).

Abbreviations: SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy.

These patients were also treated with cobalt sources 5 to 7 years after installation in 1987. The current series represents patients treated with a higher dose rate (new cobalt sources installed in 1996), despite the use of MRI data, less marginal and maximal dose prescriptions, and multiple shots yielding high conformality.

In a recently reported prospective SRT series, hearing loss was higher, although at 5 years not significantly different from an untreated observation group (53% vs. 31%), suggesting that SRT may be preferable to a policy of observation for purposes of hearing preservation. The current series agrees closely with the SRT technique and results of Kagei *et al.* (74). Based on radiobiologic principles, it is possible that a greater likelihood of hearing preservation is associated with stereotactic dose fractionation not exceeding a conventional 2-Gy dose per fraction (6, 7, 9, 78). Following radiation injury threshold data for the optic nerves (82), we have recently dropped the SRT dose per fraction to 1.8 Gy to a total of 50 Gy over 5 weeks.

When assessing hearing preservation rates after treatment, other variables may be important. Our observations reflect a significantly greater probability of hearing preservation in patients with pre-treatment G-R I hearing (Fig. 8c), suggesting that early intervention without observation may be a favorable variable (84). The higher preservation rates noted in the SRT group may simply reflect a greater number of patients with G-R I hearing before treatment. When G-R I patients were compared by treatment group, however, SRT patients with pre-treatment G-R Grade I hearing had a significantly greater probability of maintaining serviceable hearing after treatment than did SRS patients (Fig. 8d). These data support immediate treatment of G-R I patients with conventional fraction SRT yielding the highest probability of functional hearing preservation.

Another important variable is the means by which audiometric data are gathered and assessed. We attempted to obtain immediate pretreatment audiograms whenever possible, but we accepted audiograms obtained 4 to 6 months before treatment in both treatment groups. It is possible that patients with hearing rated as serviceable had, by Gardner-Robertson criteria, dropped below a Grade 2 level by treat-

ment. When evaluating hearing in the post-treatment period, we relied on audiograms performed at different institutions that undoubtedly differed in testing techniques. As a rule, audiograms were considered reliable when speech reception thresholds approximated the pure tone average.

Although lower than for sporadic tumors, a 67% hearing preservation rate with a satisfactory tumor control rate at a 2-year mean follow-up was nonetheless achieved in NF-2 patients, a rate improved from surgical series (68) and earlier SRS series (85) and consistent with more recently reported SRS NF-2 series (86, 87) (See Table 7). A recently reported series from Pittsburgh describes an outstanding 98% tumor control rate in 35 NF-2 patients with 40 tumors (54). The authors feature a 43% hearing preservation rate that increased to 67% in the subgroup of patients treated according to modern radiosurgery techniques, including treatments based on MRI data. Since tumor volumes were not specified and represent a variable of unclear significance, a comparison with the current series remains speculative, and future accrual of NF-2 patients treated by both techniques will be necessary to assess which technique best serves this challenging patient population.

We have analyzed complications and responses of 125 patients receiving either SRS or SRT. We conclude that both techniques achieve excellent outcomes with low morbidity and comparable rates of trigeminal and facial nerve preservation. As one notable exception, SRT achieved a 2.5-fold higher rate of hearing preservation in sporadic tumor patients with serviceable hearing, a rate superior not only to SRS, but also to microneurosurgery and the natural history. This assertion is compelling based on audiometric data with a longer follow-up interval. Both SRS and SRT techniques achieve a high tumor control rate in NF-2 tumors, although SRT to 50 Gy is less efficacious. Perhaps a higher total dose will be necessary to achieve a higher NF-2 tumor control rate with SRT, but hearing preservation rates may fall as a result. In a recent publication, we suggested an algorithm for the treatment of acoustic tumors that includes up-front radiosurgical intervention (7). Longer follow-up and larger patient accrual using both SRS and SRT techniques should refine this decision analysis.

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