Multisession stereotactic radiosurgery for large vestibular schwannomas

Leopoldo Casentini, MD,¹ Umberto Fornezza, MD,¹ Zeno Perini, MD,¹ Egle Perissinotto, ScD,² and Federico Colombo, MD¹

¹Center of Stereotactic Radiosurgery, S. Bortolo City Hospital, Vicenza; and ²Department of Cardiac, Thoracic, and Vascular Sciences, Padua University, Padova, Italy

OBJECT Microsurgery is not the only option for larger vestibular schwannomas (VSs); recent reviews have confirmed the feasibility and efficacy of radiosurgery for larger VSs. This study illustrates the outcomes of a series of large VSs after multisession stereotactic radiosurgery (SRS).

METHODS A series of 33 VSs larger than 8 cm³ (range 8–24 cm³, mean 11 cm³, median 9.4 cm³) were treated using the CyberKnife from 2003 to 2011 with the multisession SRS technique in 2–5 fractions (14–19.5 Gy). Five patients had undergone surgical removal and 5 had ventriculoperitoneal shunts. Nine patients were eligible for but refused surgery. Twelve patients were older than 70 years and 5 were younger than 40 years. Two female patients had neurofibromatosis.

RESULTS The follow-up period ranged from 12 to 111 months (median 48 months); radiological growth control was achieved in 94% of cases: 19 tumors (58%) displayed no size variation or reduction in tumor diameter; 12 (36%), after a transient enlargement, presented with arrested growth or shrinkage. Seven patients had a volume reduction of more than 50%. Two patients (6%) needed debulking and 2 were treated with ventriculoperitoneal shunts. Actuarial progression-free survival rates at 1 year and 5 years were 97% and 83%, respectively. Hearing was retained in 7 of the 8 patients with serviceable baseline hearing. Adverse events were limited to 1 case each of vertigo, tongue paresthesia, and trigeminal neuralgia.

CONCLUSIONS The good control rate obtained with multisession SRS deepens the controversy of the radiobiology of VSs and may extend the indication of radiation therapy (fractionated or SRS) for large VSs to include patients without symptoms of mass effect. The limited number of cases and short follow-up period do not provide sufficient support for widespread application of multisession SRS in young patients. Further studies with multisession SRS are warranted.

<http://thejns.org/doi/abs/10.3171/2014.11.JNS131552>

KEY WORDS CyberKnife; multisession radiosurgery; stereotactic radiosurgery; vestibular schwannoma; radiosensitivity; α/β ratio

VESTIBULAR schwannomas (VSs) are benign tumors arising from the vestibulocochlear nerve. These tumors may be isolated or associated with neurofibromatosis (NF), and they represent about 10% of all brain tumors,⁴³ with an incidence of 1/100,000 per year.⁸ They can have intracanalicular or extracanalicular localization with extension at the cerebellopontine angle. They are slow-growing tumors with a rate of progress between 0 and 3.9 mm per year.^{19,37,38} Nevertheless, their clinical signs and symptoms may prove debilitating, involving the fifth (trigeminal), seventh (facial), and eighth (acoustic)

pairs of cranial nerves. The most common symptoms include an ipsilateral hearing loss, which may be of varying severity up to complete deafness, tinnitus, and dizziness; signs of brainstem compression and hydrocephalus appear with larger tumors. Usually the diagnosis is made using CT or MRI to investigate the occurrence of sensorineural hearing loss documented by audiometry and auditory brainstem response; not infrequently, the slow progression is ignored and the diagnosis is made some years after the onset of symptoms.

Standard therapeutic strategies for VSs are surgical re-

ABBREVIATIONS BED = biologically effective dose; IQR = interquartile range; NF = neurofibromatosis; SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

SUBMITTED August 2, 2013. **ACCEPTED** November 18, 2014.

INCLUDE WHEN CITING Published online January 16, 2015; DOI: 10.3171/2014.11.JNS131552.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

moval, stereotactic radiosurgery (SRS), and, with small tumors, a wait-and-scan policy.^{2,12} Microsurgery is the first option if the tumor is large or symptoms of mass effect and hydrocephalus are present.^{4,21,35,36} SRS is generally used to treat small- to medium-sized VSs but has also demonstrated satisfactory results with larger lesions as well.^{20,30,31,39–41,45} Nevertheless, the latter represent a challenge for both surgeons and radiosurgeons, because a direct correlation between tumor size and facial nerve damage does exist in the postoperative period. Furthermore, the current standard therapeutic dose (12–13 Gy) may be too high and not well tolerated by healthy surrounding nervous structures, with potential adverse radiation effects, without effecting rapid volume reduction.^{3,42} Multisession stereotactic radiosurgery (SRS)^{1,5,6,13,17} performed using the CyberKnife (Accuray Inc.) in 2–5 fractions has been the main therapeutic choice at our institution since January 2003 for patients harboring VSs. The present study will contribute to the debate on the therapeutic strategies for VSs, by showing disease outcomes following multisession SRS in a series of patients with lesions larger than 8 cm³.

Methods

Between 2003 and 2011, we used the CyberKnife to treat 33 patients affected by large VSs, the volume of which varied from 8 to 24 cm³ (mean 10.97 cm³, median 9.4 cm³). All tumors were Grade 4 according to the Koos classification.²¹

Volumes were calculated using the MultiPlan (Accuray) planning system during treatment or using the treatment planning records; on MR or CT images, the formula $(D1 \times D2 \times D3)/2$ was adopted, where D1 was the major anteroposterior axis parallel to the petrous bone, D2 was the major axis orthogonal to D1, and D3 was the major craniocaudal axis.

The study included 18 women and 15 men ranging in age from 28 to 85 years (mean 63 years, median 67 years at time of treatment). Five patients had undergone previous incomplete resection or had experienced recurrence and 5 patients had prior ventriculoperitoneal shunt placement. Twelve patients (36%) were older than 70 years, 9 were 60–70 years; the remaining patients were younger but were affected by comorbidities. Nine patients (27%), 6 of whom were younger than 60 years, were eligible for but refused surgery. Two female patients (28 and 33 years old) were affected by NF Type 2. All but 4 patients presented after more than 1 year between the beginning of symptoms and radiosurgery. Eight patients had markedly deteriorated but still serviceable hearing (Gardner-Robertson Grade II).¹⁰ The remaining patients' hearing ranged from Grade III to complete deafness (Grade V). The patients who had previously undergone surgery had no hearing ability. Regarding other symptoms, there were 7 cases of facial numbness, 9 cases of facial weakness (in 2 patients with Grade IV, 1 with Grade III, and 6 with Grade II according to the House-Brackmann facial nerve scale¹⁵), 20 cases of tinnitus, and 4 cases of vertigo. Symptoms of mass effect and brainstem compression were not included; such symptoms were considered a contraindication to radiosurgery.

Treatment

The number of fractions varied from 2 to 5 (2 fractions in 1 patient, 3 fractions in 24 patients, 4 fractions in 3 patients, and 5 fractions in 5 patients). The collimator sizes used were 7.5 mm in 1 case, 10 mm in 13 cases, 12.5 mm in 13 cases, and 15 mm in 6 cases. The nonisocentric, conformal treatment planning modality was adopted in all cases. The prescription dose ranged from 14 to 19.5 Gy; maximum doses were 18.75–25.78 Gy. Prescription isodose lines were 70% (6 cases), 75% (6 cases), 80% (18 cases), 85% (2 cases), and 82% (1 case).

The marginal dose, collimator, and fractionation scheme were chosen to achieve at least 90% tumor coverage and a brainstem dose not exceeding 15 Gy (in 3 fractions), 16 Gy (in 4 fractions), or 17.5 Gy (in 5 fractions).

The biologically effective dose (BED), based on the linear-quadratic model²⁵ ($BED = nd[1 + (d/\alpha/\beta)]$, where n is the number of fractions and d is the dose per fraction) ranged from 38.5 to 72 Gy assuming an α/β ratio of 2 Gy for VS. Patient characteristics by fractionation groups are shown in Table 1.

Follow-Up

The follow-up period ranged from 12 to 111 months. MRI or CT scanning (one patient had a pacemaker and another underwent emergency CT scanning) was performed every 6 months for the first 3 years after treatment and once a year after that. The usual clinicoradiological interval of 6 months during the first 3 years after the treatment was disregarded in some instances and more frequent examinations were conducted to monitor any tumor swelling and the ventricular dimensions. Growth control was monitored by measurements performed on contrast-enhanced T1-weighted MRI with the formula $(D1 \times D2 \times D3)/2$.

We considered the cases with no enlargement or reduction of the tumor diameters detectable on neuroradiological follow-up beyond a margin of error as “controlled” disease. This is a generally accepted criterion,^{14,22,24,27,30,45} even though stability of tumors that may present after long periods of quiescence can be a misleading appearance of success. A 1-mm-diameter change results in a volume difference of about 10%. Cases in which transient tumor growth, 12–30 months after radiosurgery, was followed by cessation of the growth or shrinkage were classified as disease with delayed control while a persistent enlargement of the lesion 24–36 months after multisession SRS, requiring surgical removal, identified disease progression.

Statistical Analysis

Qualitative data were described using unconditional or conditional distributions. The counts and percentages were computed. Quantitative variables were described using the median and interquartile range (IQR). Proportions were compared using the chi-square test. The statistical significance of differences among median values of patients with controlled disease and delayed control were tested using the Wilcoxon rank-sum test.

To show the evolution of the disease, the number of cases with reduced, stable, or increased tumor dimensions

TABLE 1. Patient characteristics and treatment overall and by number of fractions*

Variable	Total Sample (n = 33)	2–3 Fractions (n = 25)	4 Fractions (n = 3)	5 Fractions (n = 5)
Sex†				
Female	18 (54.5)	12 (48)	3 (100)	3 (60)
Male	15 (45.5)	13 (52)	0 (0)	2 (40)
Median age in yrs	67 (57–73)	65 (53–72)	69 (59–80)	74 (65–79)
Median lesion vol in cm ³	9.4 (8.3–12.0)	9.3 (8.1–10.7)	10.4 (9.4–17.7)	13.4 (9.6–13.4)
Median isodose in cGy	1750 (1600–1800)	1750 (1600–1800)	1520 (1400–1680)	1949 (1937–2000)
Median BED in Gy	66.2 (57.5–71.3)	68.5 (63.8–72.0)	44.0 (38.5–52.0)	57.5 (56.9–60.0)

* Median values are presented as the median (IQR).

† Presented as the number of patients (%).

was computed at each year after multisession SRS. Moreover, the probability of disease progression-free survival over time was modeled using the Kaplan-Meier survival method.

For each statistical test, the significance level was set at 0.05.

Results

Tumor Control

Over a median follow-up of 48 months after multisession SRS (1167 patient-months on the whole), the proportion of patients with controlled disease was 58% (19 patients). Among them, 13 tumors (68%) were smaller after treatment, and 6 (32%) were stable. Six of the 19 patients showed more than 50% reduction compared with the baseline volume (Figs. 1 and 2).

During the follow-up, 12 patients (36%) were classified as having delayed disease control. Seven patients exhibited cessation of tumor growth in a period between 12 and 18 months after treatment, while 5 patients showed shrinkage of the lesion (in 1 case reaching more than 50%) over a period of up to 30 months. Two of the 7 patients underwent ventriculoperitoneal shunt placement. In one of these patients, the shunt was inserted at 8 months after multisession SRS and MRI showed a reduction of the lesion at 12 months. In the other patient, the drain was inserted at 13 months and MRI showed that the lesion did not have further progression at 18 months.

Two patients (6%) had tumor progression. Both underwent surgical tumor removal, one patient at 48 and the other at 82 months after SRS treatment. In the first patient, the VS gradually increased from a volume of 8 cm³ to 17.9 cm³ without causing remarkable clinical signs except hearing reduction, but causing important distortion of the brainstem without hydrocephalus. In the other patient, the enlargement of the tumor started 60 months after SRS treatment (this patient had NF Type 2 and was the only patient treated with 2 fractions; this case suggests that VS patients need lifelong monitoring).

The characteristics of patients in the controlled disease, delayed control, and disease progression groups are shown in Table 2. The patients with disease progression were young women, but the small number of patients did not allow for any statistical assessment. In Fig. 3, the distribution of the patients with controlled disease, delayed

control, and disease progression at each year after multisession SRS in comparison with the previous follow-up time is shown. Notably, all patients with delayed control achieved controlled disease within the 3rd year posttreatment. The Kaplan-Meier plot in Fig. 4 shows that actuarial progression-free survival rates at 1 and 5 years were 97% and 83%, respectively.

One patient died during follow-up. He was an 83-year-old man whose lesion was growing in the 2 years preceding irradiation. Two years after treatment, the VS seemed unchanged. However, 45 months after treatment, at the age of 86 years, this patient, who had previous cardiovascular problems, experienced heart failure. At admission to the hospital, he underwent CT scanning without contrast to rule out complications such as hydrocephalus or hemorrhage related to VS. The examination showed a marked shrinkage of the schwannoma.

Clinical Control

Hearing capacity was preserved in 7 of the 8 patients with Gardner-Robertson Grade II hearing. The patient who lost her serviceable hearing experienced tumor volume progression from 8 to 17.9 cm³ and underwent surgical removal 48 months after multisession SRS. One of the patients who remained with Grade II hearing required a ventricular shunt 13 months after multisession SRS.

FIG. 1. Magnetic resonance images obtained in a 59-year-old woman before radiosurgery (4 fractions, BED 52 Gy; **left**) and at the 8-year follow-up examination (**right**).

FIG. 2. Magnetic resonance images obtained in a 79-year-old man before radiosurgery (5 fractions, BED 50.4; **left**) and at the 4-year follow-up examination (**right**).

Other symptoms present at the time of treatment stabilized during follow-up; only 2 patients had complete relief from vertigo and 1 patient had a reversal of facial paresis. We registered worsening clinical status—an onset of vertigo, a case of paresthesia in the tongue, and a trigeminal neuralgia—in 3 patients. In addition, 30 months after multisession SRS, a 77-year-old female patient developed polyneuritis causing paraparesis; 22 months after treatment a 67-year-old male patient suffered low-back pain, and MRI revealed spinal schwannomas at T-11 and L-2 that required surgery.

Discussion

A limited number of studies on radiosurgery as the primary treatment for large vestibular schwannomas have been conducted (Table 3), and microsurgery is generally considered the first choice.^{4,14,16,22,32,45} In a recent publication, Yang et al. concluded that if the patient is asymptomatic, the tumor is smaller than 10 cm³, and/or the Koos

FIG. 3. Number of patients with reduced, stable, and increased VS dimensions after treatment, by years.

grade is less than 4, SRS could be the first choice of treatment more likely to lead to tumor regression.⁴⁵ A similar conclusion was presented by van de Langenberg et al.³⁹ in the first part of a recent study: radiological growth control was achieved in nearly 90% of cases in both series. In his editorial, Kondziolka affirmed—in the absence of ataxia, disabling headache, hydrocephalus, or refractive fifth cranial nerve neuralgia—SRS is a practical option.¹⁹

The single-fraction high-dose technique, according to radiobiological experience, is the best option for treating slow-growing lesions that respond late to radiation therapy.^{25,42} These lesions should respond to a single, high-dose radiation better than to a conventionally fractionated dosage (50–55 Gy in 25–30 fractions). Like bone and nervous tissue, arteriovenous malformations, meningiomas, and neuromas are late responders, and their α/β ratio is generally considered low, where coefficient α represents a lethal single-impact injury and coefficient β a lethal injury due to accumulation of sublethal doses. Early-responding tissues (bowel mucosa, skin, and bone marrow) and rapidly proliferating tumors, e.g., lymphomas, have a high α/β ratio (more than 5).²⁵ Standard fractionation is more effective for early-responding tumors. Nevertheless, despite the

TABLE 2. Patients' features stratified by disease status*

Variable	Controlled Disease (n = 19)	Delayed Control (n = 12)	Disease Progression (n = 2)	p Value†
Sex‡				0.89
Female	10 (52)	6 (50)	2 (100)	
Male	9 (48)	6 (50)	0 (0)	
Age in yrs	Median 65 (59–77)	Median 68 (50–73)	33, 45	0.82
Lesion vol in cm ³	Median 9.5 (8.3–13.4)	Median 9.4 (8.4–11.6)	8, 12	0.69
Isodose in cGy	Median 1725 (1520–1790)	Median 1800 (1750–1904)	1440, 1790	0.03
BED in Gy	Median 63.8 (50.4–68.5)	Median 68.5 (59.3–72.0)	66.2, 71.3	0.12
Fractions‡				0.94
≤3	14 (74)	9 (75)	2 (100)§	
>3	5 (26)	3 (25)	0 (0)	
Follow-up length in mos	Median 48 (24–60)	Median 24 (24–42)	48, 72	0.13

* Median values are presented with the IQR in parentheses.

† Comparison between controlled disease and delayed control groups by means of Wilcoxon test or chi-squared test.

‡ Values are number of patients (%).

§ Two fractions in one patient and 3 fractions in the other.

FIG. 4. Kaplan-Meier plot showing the probability of controlled disease during follow-up.

radiobiological expectations based on α/β calculations, excellent results have been obtained also by fractionated SRS and fractionated stereotactic radiotherapy (50–55 Gy in 25–30 fractions) for VS, with control rates of 90%–95%.^{5,11,18,22,23,25,27,29,44} In light of these seemingly paradoxical data, we made a comparison between the conventional-dose SRS and the dose of multisession SRS in our series.

A marginal dose of 12 Gy is generally considered sufficient and safe in radiosurgical practice, and, from a radiobiological standpoint, SRS is the gold standard for the treatment of VSs.^{14,27,30} In hypofractionated schedules, a prescription dose of 18 Gy in 3 fractions corresponds to 11 Gy in a single fraction, if we accept that the α/β ratio of neuromas is low, about 2 Gy. If we analyze our results (Table 4), we note that the patients in the controlled disease and delayed controlled disease groups who were treated in 3 fractions received a mean prescription dose of 17 Gy, corresponding to 10.5 Gy of SRS if the α/β ratio of VS is 2 Gy or a little higher. Based on this hypothesis, our VSs would be underdosed, but then why would they display a clear regression or stabilization? Could it be that, under certain circumstances, neuromas had an α/β ratio higher than is generally believed? If the ratio were 10, the traditional dose of 12 Gy of SRS (Table 5) would correspond to 16.8 Gy delivered in 3 fractions, or 18 Gy in 4 fractions, or 19 Gy in 5 fractions. If the α/β ratio were 5, the com-

TABLE 4. Mean marginal dose in patients with controlled disease and delayed control and correspondence with single-shot SRS

No. of Fractions (no. of patients)	Mean Marginal Dose (Gy)	Correspondence w/ Single-Shot SRS		
		If $\alpha/\beta = 2$	If $\alpha/\beta = 5$	If $\alpha/\beta = 10$
3 (24)	17	10.5 Gy	11 Gy	12 Gy
4 (3)	15.33	<9 Gy	<10 Gy	<11 Gy
5 (5)	19.37	10 Gy	11 Gy	<13 Gy

mon schedule of 18 Gy in 3 fractions would correspond to a little less than a single 12-Gy fraction of SRS. The same would be true also for the 5 patients who were treated with 5 fractions with a total dose of 19 Gy, corresponding to a 12-Gy single-fraction equivalent if the α/β ratio of VSs were 10. Vernimmen and Slabbert calculated the BED for VSs in various dose fractionation schedules. According to their calculated BED, for an α/β ratio higher than 5, every fractionation regimen resulted in a more advantageous risk/benefit ratio than that obtained with a single fraction of 12 Gy.⁴²

Our data suggest that the radiobiology of VSs is still unclear; genetic markers determining radiosensitivity need further investigation.⁴⁶ In any case, various reports demonstrate that SRS or fractionated stereotactic radiotherapy can achieve a tumor control rate of about 90%–96% treating VS,^{7,9,14,16,18,23,28,29,33,34} and a small percentage of progressive VSs after irradiation tend to exist in every study group. So far, we are unable to predict, on the basis of clinical history, neurological status, and neuroradiological and functional investigations, whether a particular patient will belong to the category of responders or nonresponders.

It has been recently suggested that multisession SRS, compared with single-fraction radiosurgery, results in better hearing preservation and, in the case of larger VSs, fewer side effects due to better sparing of the normal tissues and organs at risk.¹³

We wish to emphasize the following points: 1) multisession SRS should not necessarily be limited to elderly patients harboring large VSs or patients affected by comorbidities. Further experiences with larger numbers of young patients and longer follow-up controls are needed to recommend multisession SRS for young people af-

TABLE 3. Radiosurgical treatment of large VSs in the literature

Authors & Year	No. of Cases	Tumor Size	Type of Radiosurgery	Mean Diameter or Vol	Follow-Up (mos)	Growth Control
Lederman et al., 1997	16	>3 cm	LINAC/MRS	3.7 cm	Median 20.7	16/16
Prasad et al., 2000	19	>6.5 cm ³	GKS	NR	Mean 50	18/19
Rowe et al., 2003	35	>3 cm	GKS	NR	Mean 35	30/35
Litvack et al., 2003	9	>3 cm	GKS	NR	Mean 31.7	9/9
Inoue, 2005	18	>3 cm	GKS	15.2 cm ³	Range 72–156	14/15
Hasegawa et al., 2005	24	>15 cm ³	GKS	NR	Median 93	13/24
Mandl et al., 2010	25	>3 cm	LINAC/MRS	NR	Mean 36	21/25
Yang et al., 2011	65	>3 cm	GKS	9 cm ³	Median 36	59/65
van de Langenberg et al., 2011 ⁴¹	33	>6 cm ³	GKS	8.8 cm ³	Median 30	29/33
Present study	33	≥8 cm ³	CyberKnife/MRS	11 cm ³	Range 12–111	31/33

GKS = Gamma Knife surgery; LINAC = linear accelerator; MRS = multisession radiosurgery; NR = not reported.

TABLE 5. Correspondence between therapeutic dose (12 Gy) of SRS and various multisession SRS schedules depending on different hypothetical α/β ratios

No. of Fractions	$\alpha/\beta = 2$	$\alpha/\beta = 5$	$\alpha/\beta = 10$
3	19.8 Gy	18.3 Gy	16.8 Gy
4	22.4 Gy	20.4 Gy	18 Gy
5	24.5 Gy	22 Gy	19 Gy

affected by large VSs; long-term tumor control and malignant transformation are matters of concern.²⁶ In our series, only 5 patients were younger than 40 years; one of them underwent surgery after progression, another was in the controlled disease group, and 3 were in the delayed control group. 2) A “large” VS, in the absence of critical clinical symptoms, does not necessarily require surgical removal or debulking. 3) An interdisciplinary evaluation involving neurosurgeons, otolaryngologists, and radiation oncologists could determine the best treatment option based on the experience of the surgical team and the available technological facilities. 4) A strict clinical/radiological follow-up is essential.

This retrospective study has certain limitations, such as risk of selection bias, a wide range of follow-up periods (12–111 months), and a small number of patients, particularly young people. Nevertheless, a significant number of patients (18 of 33) had up to a 48-month follow-up, over which the sample size decreased rapidly.

Conclusions

In our experience, multisession SRS is a reliable therapeutic strategy for larger VSs in absence of mass effect symptoms. The satisfactory growth control obtained with lower doses compared with traditional SRS raises the issue of the radiosensitivity of VS.

Acknowledgments

Leopoldo Casentini thanks Mikail H. Gezginci, MPharm, PhD, for his helpful, kind reviewing of the manuscript and Simone Chiapperin for technical support.

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Author Contributions

Acquisition of data: Casentini, Fornezza, Perini, Colombo. Analysis and interpretation of data: Casentini, Colombo. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Casentini. Statistical analysis: Perissinotto. Administrative/technical/material support: Perini. Study supervision: Colombo.

Supplemental Information

Previous Presentation

This work was partially presented as proceedings at the First European Conference on SRS/SBRT and IG-IMRT, “Radiation Oncology: can we still treat without image guidance?” Milan, Italy, February 22–23, 2013.

Correspondence

Leopoldo Casentini, Ospedale S. Bortolo, UO Neurochirurgia 2-Radiocirurgia, Viale Rodolfi 37, Vicenza 36100, Italy. email: casentini.leopoldo@libero.it.