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Therapeutic profile of single-fraction radiosurgery of vestibular schwannoma: unrelated malignancy predicts tumor control

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Radiosurgery has become an accepted treatment option for vestibular schwannomas. Nevertheless, predictors of tumor control and treatment toxicity in current radiosurgery of vestibular schwannomas are not well understood. To generate new information on predictors of tumor control and cranial nerve toxicity of single-fraction radiosurgery of vestibular schwannomas, we conducted a single-institution long-term observational study of radiosurgery for sporadic vestibular schwannomas. Minimum follow-up was 3 years. Investigated as potential predictors of tumor control and cranial nerve toxicity were treatment technology; tumor resection preceding radiosurgery; tumor size; gender; patient age; history of cancer, vascular disease, or metabolic disease; tumor volume; radiosurgical prescription dose; and isodose line. Three hundred eighty-six patients met inclusion criteria. Treatment failure was observed in 27 patients. History of unrelated cancer (strongest predictor) and prescription dose significantly predicted tumor control. The cumulative incidence of treatment failure was 30% after 6.5 years in patients with unrelated malignancy and 10% after ≥15 years in patients without such cancer ($P < .02$). Tumor volume was the only predictor of trigeminal neuropathy (observed in 6 patients). No predictor of facial nerve toxicity was found. On the House and Brackmann scale, 1 patient had a permanent one-level drop and 7 a transient drop of 1 to 3 levels. Serviceable hearing was preserved in 75.1%. Tumor hearing before radiosurgery, recurrence, and prescription isodose predicted ototoxicity. Unrelated malignancy is a strong predictor of tumor control. Tumor recurrence predominantly predicts ototoxicity. These findings potentially will aid future clinical decision making in ambiguous cases.

Keywords: cyberKnife, Gamma Knife, radiosurgery, stereotactic radiation therapy, unrelated malignancy, vestibular schwannoma.

After an evolution of more than 3 decades, stereotactic radiosurgery has become an internationally accepted treatment option for vestibular schwannomas.[1–8] Radiosurgery is attractive because of its high efficacy and low toxicity. Yet, the predictors of tumor control and treatment toxicity have not been studied in detail, especially in the cases of modern treatment technologies and at currently established lower radiation doses.

With this study, we wish to generate new information on predictors of tumor control and cranial nerve toxicity of single-fraction radiosurgery of vestibular schwannomas. Along with clinical and dosimetric factors, outcomes obtained with 2 different treatment technologies were investigated.

Patients and Methods

This study included patients with sporadic vestibular schwannomas and at least 3 years of follow-up after radiosurgery. Consecutive patients were treated between 1995 and 2008. Radiosurgery was applied either as primary treatment or, in the case of residual or recurrent tumors, after surgical resection. Patients with neurofibromatosis were excluded. Tumor volume was limited to 15 cm^3. Patients with better hearing in the tumor-affected ear were excluded from the ototoxicity analysis. All patients were treated with a single fraction.[9,10] Diagnostic findings, treatment parameters, and follow-up data were stored prospectively in a database (FileMaker Pro 8.0v1). Follow-up included physical

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examination, magnetic resonance imaging (MRI), and audiometry when measurable.

Treatment Procedure

Outpatient radiosurgery was performed as described.[11,12] Either Gamma Knife (Elekta AB)[13] or CyberKnife (Accuray)[14] was used. Gamma Knife is a frame-based radiosurgery device.[13] The therapeutic radiation is emitted by 201 ^{60}cobalt sources situated in a fixed array on a spherical segment and projecting to a single isocenter. GammaPlan Software is able to calculate highly conformal dose plans with steep dose gradients. Treatment is delivered by sequentially moving the isocenter on the tumor. Single- and multiple-isocenter treatment leads to inhomogeneous dose distributions. For vestibular schwannomas, a median of 7 isocenters (range, 1–27) was used for dose delivery.

CyberKnife is a frameless, image-guided robotic radiosurgery system.[14] The therapeutic radiation is generated by a small linear accelerator mounted on the robotic arm. Treatment planning was performed with the MultiPlan software. Radiosurgery with CyberKnife administered a non-coplanar, non-isocentric treatment plan, which allowed the delivery of a more homogeneous dose distribution—compared with that from a Gamma Knife plan—with a steep dose gradient. For vestibular schwannomas, a median of 149 beams (range, 49–332) was used for dose delivery.

Statistical Analysis

The Stata/IC 12.1 software package was used. To determine tumor control, we applied cumulative failure function and competing-risk regression analysis. Diagnosis of failure was the event of interest, and patients were censored at the time of last clinical follow-up if they had not failed. Patients who died were censored at the date of their death; patients who were $\geq$70 years old at the time of their latest follow-up and who were not followed up for >3 years between the latest follow-up and the study end (January 31, 2012) were categorized as lost to further follow-up. These patients were censored at the date of their latest follow-up and were included in the competing-risk regression analysis. In patients <70 years of age, an interval of 5 years between the latest follow-up and the study end was accepted; otherwise, they were censored as well.

As appropriate, multiple regression models were calculated to identify predictors of cranial nerve function before radiosurgery and toxicity (after treatment). Significance of multivariate models was assumed if $P < .01$; otherwise, the significance threshold was set to $P < .05$. A 2-sided Fisher's exact test or a Student's *t*-test was used as appropriate. The following variables were tested for predictive significance: treatment technology (Gamma Knife or CyberKnife), surgery preceding radiosurgery (eg, residual vestibular schwannomas, recurrence after surgery), the side of the tumor, patient's gender, age (y) at the time of radiosurgery, medical history of any unrelated malignant tumor (also referred to as *malignancy*), vascular disease, metabolic disease, hearing loss (dB), tumor volume (cm^3), radiosurgical prescription dose (Gy), and isodose (%). *Vascular disease* referred to any vascular indication that needed medical or surgical intervention. *Metabolic disease* referred to either diabetes mellitus or other indications affecting metabolism and requiring treatment. If not stated otherwise, numerical values indicate means, with 95% confidence intervals in parentheses. Continuous variables (age, dose, etc) were not dichotomized.

Cranial Nerve Function

Trigeminal nerve function before radiosurgery and toxicity was evaluated by physical examination; a binary scoring was applied, where 1 = a detectable trigeminal deficit and 0 = none. Facial nerve function was examined with the grading system of House and Brackmann.[15]

Hearing function was investigated by serial pure tone audiometry. Serviceable hearing was defined upon applying the pure tone audiometry component of the Gardner and Robertson classification.[16] The term *ototoxicity* refers to quantitative (dB) posttreatment hearing loss attributable to radiosurgery. This was calculated as follows: First, to determine the overall hearing loss, bilateral serial pure tone audiometry was performed including the frequencies 0.5, 1, 2, 4, and 8 kHz. Then, the net hearing loss was calculated at each frequency as the difference between the hearing thresholds of the healthy ear and the affected ear. The mean of the net hearing loss values at the frequencies of 0.5, 1, 2, 4, and 8 kHz defined the overall hearing loss (dB). Hearing loss attributable to radiosurgery was calculated in patients with testable hearing, as the difference between overall hearing loss at the time of radiosurgery and during follow-up. A cutoff of $\geq$20 dB of overall hearing loss was used to identify patients as having significant hearing loss before radiosurgery. A cutoff of $\geq$20 dB of hearing loss attributable to radiosurgery was used to identify patients as having ototoxicity. This parameter ($\geq$20 dB of hearing loss attributable to radiosurgery) was used in the cumulative incidence (failure) function and competing-risk regression analysis of predictors of ototoxicity. (Patients who died or who were lost to follow-up were censored as indicated above.) Not studied was further cranial nerve function, including that of the vestibular nerve.

Results

Patients

A total of 386 patients with vestibular schwannoma (Table 1) were included. Of these, 257 (66.6%) were treated with Gamma Knife and 129 (33.4%) with CyberKnife; 210 (54.4%) of the patients were women; mean age was 55.5 years (range, 16.4–84.9). Gamma Knife patients were significantly older than CyberKnife patients ($P < .001$). Before radiosurgery, 109 patients (28.2%) had undergone microsurgical resection.

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Table 1. Patient characteristics and treatment parameters

	All	GK	CK	*P*
Patients (no)	386	257 (66.6%)	129 (33.4%)	
Gender (f/m)	210/176	132/125	78/51	n.s.[a]
Side (left/right)	207/179	139/118	68/61	n.s.[a]
Age (y)	55.5 (54.3–56.8)	56.9 (55.3–58.3)	52.8 (50.6–55.0)	.001[b]
Surgery	109 (28.2%)	76 (29.6%)	33 (25.6%)	n.s.[a]
VD	74 (19.2%)	58 (22.6%)	16 (12.4%)	.02[a]
MD	22 (5.7%)	11 (4.3%)	11 (8.5%)	n.s.[a]
Malignancy	29 (7.5%)	18 (7.0%)	11 (8.5%)	n.s.[a]
Hydrocephalus	8 (2.0%)	7 (2.7%)	1 (0.8%)	n.s.[a]
NV deficit	51 (13.2%)	39 (15.2%)	12 (9.3%)	n.s.[a]
NVII deficit	50 (13.0%)	37 (14.4%)	13 (10.1%)	n.s.[a]
Deaf tumor ear	121 (31.3%)	90 (35.0%)	31 (24.0%)	.04[a]
HL	296 (76.7%)	204 (79.4%)	92 (71.3%)	n.s.[a]
VSvol (ccm)	1.8 (1.6 -2.0)	2.0 (1.7–2.2)	1.6 (1.3–1.9)	.04[b]
D_{min} (Gy)	12.8 (12.7–12.8)	12.9 (12.8–13.0)	12.5 (12.4–12.5)	.001[b]
Isodose (%)	58.4 (57.5–59.3)	53.5 (52.7–54.3)	68.2 (67.5–68.9)	.001[b]

Abbreviations: VD, vascular disease; MD, metabolic disease; GK, Gamma Knife; CK, CyberKnife; HL, significant hearing loss (≥20 dB of overall hearing loss before radiosurgery); NV deficit, trigeminal neuropathy; NVII deficit, facial neuropathy (facial nerve function grade III or less); VSvol, volume of VS; D_{min}, prescription dose; *P*, level of significance GK versus CK.
Mean (95% confidence interval).
[a]Fisher's exact test.
[b]Student's *t*-test.

Table 2. Predictors of trigeminal nerve function before radiosurgery

	Multivariate Logistic Regression		Univariate Test *P*
	Coefficient	*P*	
Surgery	1.56	.001	.001[a]
Side (left/right)	−0.46	n.s.	
Gender (f/m)	0.91	.01	.02[a]
Age (y)	0.03	n.s.	
Malignancy	0.36	n.s.	
MD	−1.21	n.s.	
VD	0.09	n.s.	
VSvol (cm^3)	0.25	.001	.001[b]

Abbreviations: *P*, level of significance; "surgery," resection of vestibular schwannoma before radiosurgery; MD, metabolic disease; VD, vascular disease; "malignancy," any malignant tumor unrelated to the vestibular schwannoma; VSvol, volume of VS.
Outcome variable: trigeminal neuropathy/deficit (yes/no = 51/335)
Multivariate analysis: logistic regression (significance of model $P < .0001$);
Univariate analysis: [a]Fisher's exact test; [b]*t*-test.

Table 3. Predictors of facial nerve function before radiosurgery

	Multivariate Logistic Regression		Univariate Test *P*
	Coefficient	*P*	
Surgery	4.61	.001	.001[a]
Side (left/right)	0.30	n.s.	
Gender (f/m)	0.35	n.s.	
Age (y)	0.01	n.s.	
Malignancy	0.18	n.s.	
MD	0	omitted	
VD	−0.20	n.s.	
VSvol (cm^3)	0.04	n.s.	

Abbreviations: *P*, level of significance; "surgery," resection of vestibular schwannoma before radiosurgery; MD, metabolic disease; VD, vascular disease; "malignancy," any malignant tumor unrelated to the vestibular schwannoma; VSvol, volume of VS.
Outcome variable: facial neuropathy (facial nerve function grade III or less; yes/no = 50/336).
Multivariate analysis: logistic regression (significance of model $P < .0001$).
Univariate analysis: [a]Fisher's exact test.

Seventy-four patients (19.2%) had vascular disease, 22 (5.7%) had metabolic disease, and 29 (7.5%) had a history of unrelated malignancy. The proportions of gender, tumor side, surgical resection, vascular disease, metabolic disease, and malignancy were the same among Gamma Knife and CyberKnife patients. Mean tumor volume was 1.8 cm^3 (range, 1.6–2.0 cm^3). Tumors in the CyberKnife group were significantly smaller than those in the Gamma Knife group ($P < .04$; Table 1). At time of radiosurgery, 121 patients (31.3%) were deaf, among whom 90 (35.0%) were scheduled for Gamma Knife, and 31 (24.0%) for CyberKnife treatment ($P < .04$). Two hundred ninety-six (76.7%) patients presented with significant hearing loss (Table 1). Predictors of cranial nerve function before radiosurgery are given in Tables 2–4. Surgery before

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radiosurgery was predictive of trigeminal and facial nerve deficits and significant hearing loss before radiosurgery. Female sex and tumor volume were further predictors of trigeminal nerve neuropathy (Table 2). Higher patient's age was a further weak predictor of significant hearing loss before radiosurgery (Table 4).

Radiosurgery

A patient example is shown in Fig. 1. Treatment parameters are presented in Table 1. Prescription dose was significantly lower in the CyberKnife group compared with the Gamma Knife group (Table 1). Prescription isodose line was 68.2% (range, 67.5%–68.9%) with CyberKnife and 53.5% (52.7%–54.3%) with Gamma Knife ($P < .001$).

Tumor Control

Twenty-seven patients (7.0%) failed. In the competing-risk regression analysis, dose was a weak but significant predictor of tumor recurrence (Table 5). However, malignancy (eg, history of cancer unrelated to vestibular schwannoma) was the most significant predictor of tumor recurrence (subhazard ratio 3.69; $P < .02$). While 6/29 patients (21%) with a medical history of cancer developed tumor recurrence, only 21/357 patients (6%) without such history did so (Fig. 2). The cumulative incidence of failure was 30% at 6.5 years in patients with unrelated tumor and 11% at 10.6 years without malignancy ($P < .02$; Fig. 2). Postradiosurgery vestibular schwannoma recurred in patients with a history of breast, colon, ovary, prostate, and uterus cancers; in addition, glioblastoma, lymphoma, melanoma, and seminoma histories were noted. Remaining variables were not significant. Postradiosurgically recurrent tumors were resected in 15 patients and radiosurgically re-treated in 12.

Table 4. Predictors of hearing function before radiosurgery

	Multivariate Logistic Regression		Univariate Test *P*
	Coefficient	*P*	
Surgery	3.35	.001	.001[a]
Side (left/right)	−0.20	n.s.	
Gender (f/m)	−0.24	n.s.	
Age (y)	0.04	.001	.001[b]
Malignancy	−0.72	n.s.	
MD	0.31	n.s.	
VD	−0.03	n.s.	
VSvol (cm^3)	0.11	n.s.	.02[b]

Abbreviations: *P*, level of significance; "surgery," resection of vestibular schwannoma before radiosurgery; MD, metabolic disease; VD, vascular disease; "malignancy," any malignant tumor unrelated to the vestibular schwannoma; VSvol, volume of VS.
Outcome variable: hearing loss of ≥20 dB at the side of the vestibular schwannoma when compared with the healthy ear (yes/no = 296/90).
Multivariate analysis: logistic regression (significance of model $P < .0001$).
Univariate analysis: [a]Fisher's exact test; [b]*t*-test.

Toxicity

Eight patients (2.1%) developed new or worse but transient trigeminal toxicity symptoms. Despite this low incidence, tumor volume could be identified as the only predictive factor of trigeminal toxicity in a logistic regression analysis (coeff. 0.59; $P < .002$).

No patient suffered a complete facial nerve palsy due to radiosurgery. Facial nerve toxicity was limited to a drop of 1 to 3 levels in the House and Brackmann scale.[15] It was transient in 7 patients (1.8%); however, 1 patient (0.3%) had a permanent 1-level drop in the House and Brackmann scale.[15] This was probably due to the small number of observations; no predictive factor of facial nerve toxicity could be identified.

Serial examinations with pure tone audiometry were obtained in 165 patients for >3 years. In these patients, overall hearing loss was 21.3 dB (18.8–23.8 dB) at radiosurgery, which increased to 35.6 dB (32.0–39.2 dB) at ≥3 years follow-up and to 38.5 dB (33.2–43.7 dB) at ≥5 years follow-up. Fifty-eight (35.1%) patients developed ototoxicity (eg, ≥20 dB hearing loss attributable to radiosurgery) (Table 6). Significant hearing loss before radiosurgery (subhazard ratio 0.55; $P < .05$), recurrence (subhazard ratio 2.14; $P < .001$), and prescription isodose (subhazard ratio 0.94; $P < .02$) predicted ototoxicity (Table 6). The incidence of ototoxicity amounted to 50% at 2 years after radiosurgery in patients who experienced tumor recurrence, and at 10 years in successfully treated patients ($P < .001$; Fig. 3). A serviceable hearing[16] was preserved in 124 patients (75.1%). No patient with testable hearing before radiosurgery became deaf afterward.

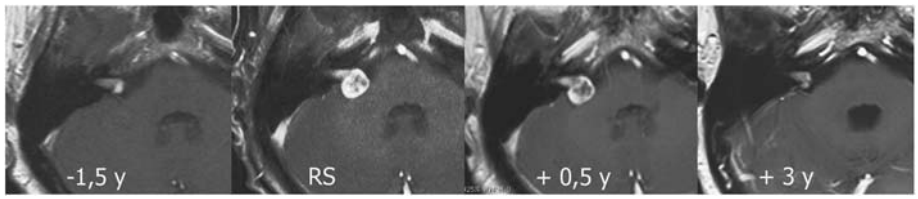

Fig. 1. Serial axial T1-weighted contrast-enhanced MRIs of a vestibular schwannoma in the right ear. Radiosurgery was performed with CyberKnife. Tumor volume was 1.1 cm^3; prescription dose was 12.5 Gy. The tumor was detected 1.5 y before treatment (left image); until the date of radiosurgery, the tumor had grown (second image from left); 6 months after radiosurgery, the tumor showed centrally decreased contrast uptake; 3 y after CyberKnife radiosurgery, the tumor significantly decreased in size (right image).

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Table 5. Predictors of tumor recurrence after radiosurgery

	Multivariate Model				Univariate Test
	SHR	SE robust	*P*	95% CI	*P*
Technology	2.89	1.80	n.s.	0.50–1.33	n.s.[a]
Surgery	1.60	0.65	n.s.	0.63–3.29	n.s.[a]
Side (left/right)	1.02	0.46	n.s.	0.39–0.24	n.s.[a]
Gender (f/m)	2.27	0.96	n.s.	1.10–5.90	n.s.[a]
Age (y)	0.97	0.02	n.s.	0.95–1.00	n.s.[b]
Malignancy	3.69	2.03	.02	1.56–12.54	.01[a]
MD	0.47	0.53	n.s.	0.05–4.29	n.s.[a]
VD	1.63	0.85	n.s.	0.52–3.90	n.s.[a]
HL	0.89	0.43	n.s.	0.37–2.63	n.s.[a]
VSvol (cm^3)	0.99	0.07	n.s.	0.87–1.14	n.s.[b]
D_{min} (Gy)	0.44	0.12	.01	0.25–0.73	.004[b]
Isodose (%)	0.98	0.03	n.s.	0.94–1.05	n.s.[b]

Abbreviations: CI, confidence interval; SHR, subhazard ratio; SE, robust standard error, standard degree-of-freedom adjustment; *P*, level of significance; "technology," Gamma Knife versus CyberKnife; "surgery," resection of vestibular schwannoma before radiosurgery; "malignancy," any malignant tumor unrelated to the vestibular schwannoma; MD, metabolic disease; VD, vascular disease; HL, significant hearing loss (≥20 dB at the side of the vestibular schwannoma when compared with the healthy ear); VSvol, volume of VS; D_{min}, prescription dose; isodose (%), prescription isodose line.
Multivariate analysis: Outcome variable: recurrence of vestibular schwannoma after radiosurgery.
Competing-risk regression analysis (significance of model $P < .0001$); no. of patients (observations): 386; no. recurrences (failed): 27; no. competing (dead/lost): 44; no. censored: 315.
Univariate analysis: [a]Fisher's exact test; [b]*t*-test.

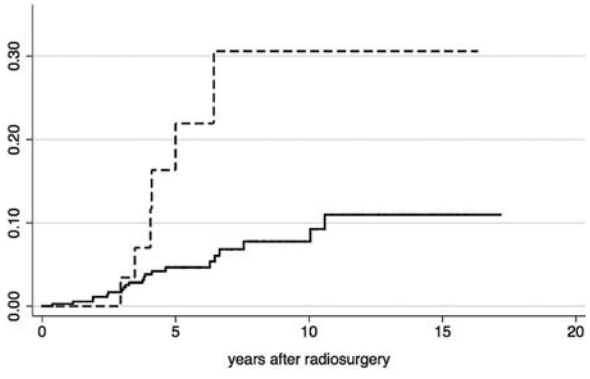

Fig. 2. Cumulative incidence of treatment failure after radiosurgery for vestibular schwannoma. In patients with malignancy (dashed line), tumor control was significantly lower compared with patients without cancer anamnesis.

Discussion

Early long-term radiosurgery outcomes for vestibular schwannoma have been published by several authors.[1,17,18] Since then, radiosurgery has become an established alternative or complement to microsurgery

Table 6. Predictors of ototoxicity after radiosurgery

	Multivariate Model				Univariate Test
	SHR	SE Robust	*P*	95% CI	*P*
Technology	1.73	0.87	n.s.	0.64–4.66	n.s.[a]
Surgery	0.74	0.60	n.s.	0.15–3.64	n.s.[a]
Side (left/right)	1.56	0.46	n.s.	0.87–2.78	n.s.[a]
Gender (f/m)	1.02	0.29	n.s.	0.59–1.78	n.s.[a]
Age (y)	0.98	0.02	n.s.	0.95–1.00	n.s.[b]
Malignancy	2.04	1.22	n.s.	0.62–6.65	n.s.[a]
MD	1.30	0.82	n.s.	0.38–4.47	n.s.[a]
VD	1.22	0.54	n.s.	0.52–2.90	n.s.[a]
HL	0.55	0.16	.05	0.31–1.00	n.s.[a]
VSvol (cm^3)	0.97	0.08	n.s.	0.82–1.14	n.s.[b]
D_{min} (Gy)	1.26	0.40	n.s.	0.67–2.36	n.s.[b]
Isodose (%)	0.94	0.02	.01	0.91–0.98	.02[b]
[§]recurrence	2.14	0.40	.001	1.49–3.09	.01[a]

Abbreviations: SHR, subhazard ratio; SE, robust standard error, standard degree-of-freedom adjustment; *P*, level of significance; "technology," Gamma Knife versus CyberKnife; "surgery," resection of vestibular schwannoma before radiosurgery; "malignancy," any malignant tumor unrelated to the vestibular schwannoma; MD, metabolic disease; VD, vascular disease; HL, significant hearing loss (≥20 dB at the side of the vestibular schwannoma when compared to the healthy ear); VSvol, volume of VS; D_{min}, prescription dose; Isodose (%), prescription isodose line.
Multivariate analysis: Outcome variable: ototoxicity after radiosurgery (a cutoff of ≥20 dB of hearing loss attributable to radiosurgery identified patients as having ototoxicity).
Competing-risk regression analysis with [§]time-varying covariate (eg, tumor recurrence; significance of model $P < .001$); no. of patients (observations): 165; no. recurrences (failed): 58; no. competing (dead/lost): 10; no. censored: 97.
Univariate analysis: [a]Fisher's exact test; [b]*t*-test.

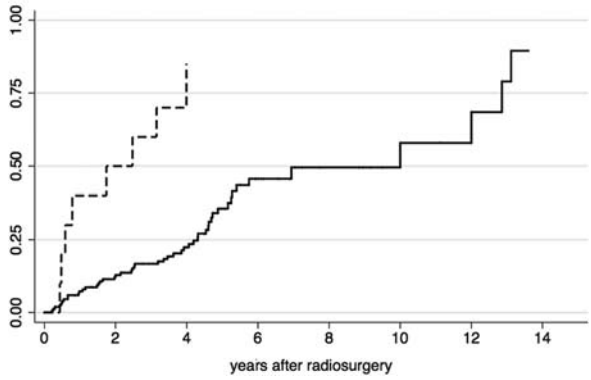

Fig. 3. Cumulative incidence of ototoxicity after radiosurgery for vestibular schwannoma. (A cutoff of ≥20 dB of hearing loss attributable to radiosurgery was used to identify patients as having ototoxicity.) The incidence of ototoxicity amounted to 50% at 2 y after radiosurgery in patients who experienced tumor recurrence (dashed line), and at 10 y in successfully treated patients.

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of vestibular schwannoma. Ever further progress in radiosurgery for vestibular schwannomas has been achieved in the past few years, and the requirements essential to performing a successful radiosurgical treatment have become available with several platforms (Gamma Knife,[4,6,8] various linear accelerators,[19,20] and most recently, CyberKnife[21]). Advances in MRI have enabled not only the detection of smaller tumors, but also an outstanding resolution of the structural anatomy of the cerebellopontine angle. Consequently, dosimetry and treatment planning software have become more refined. A review of long-term studies adopting a "modern" median dose level of 12–13 Gy has been published this year.[3] Despite the fact that the doses were now significantly lower than those reported in the classic papers and despite the lack of uniform reporting criteria in the specific literature,[22] high rates of long-term tumor control are still prevalent in the newest review article.[3] Tumor control after 5 and 10 years is between 91% and 100%.[3,4,8,19,20,23–25] In our study, with the same dose, tumor control was in the same order of magnitude. This is consistent with the recent literature.[3,4,8,19,20,23–25] A dose effect is evident from experimental data,[26] and we could also show a significant dose effect on tumor control. Due to the narrow dose range in the present study, this effect was less distinct but present. However, neither treatment technology, lesion side, sex, age, metabolic disease, vascular disease, vestibular schwannoma volume, nor prescription isodose line had any significant impact on tumor control. Furthermore, a medical history of unrelated malignancy had a very strong impact on vestibular schwannoma control after radiosurgery in our study. We found that patients with histories of different types of cancer had 4 times as high a risk of treatment failure as individuals without such history. This is a novel and significant finding among our results. It places a clinical spotlight on one of the biological determinants of radiosurgical outcome of benign vestibular schwannomas. The finding correlates well with the results of basic research, which have shown that the mutation of the NF2 gene—a key event in vestibular schwannoma oncogenesis—and the consecutive loss of function of its gene product, the merlin protein, can be tumorigenic with respect to schwannomas and other tumors.[27,28] Furthermore, this mutation increases radioresistance of schwannomas.[29,30] However, the exact background of these results is not fully understood and deserves further investigation.

Regarding trigeminal and facial nerve toxicity of radiosurgery, our data generally reinforce what has been critically reviewed recently.[3] Vestibular schwannoma volume and dose to the tumor margin strongly correlate with the risk of trigeminal and facial nerve neuropathy;[3] with the marginal doses of 12–13 Gy, permanent preservation of the trigeminal nerve and facial nerve has been possible in 92%–100% and 94%–100% of the cases, respectively.[3] In our study, these cranial nerves remained unaffected after radiosurgery in 98% of the cases. As in our previous study,[31] tumor volume could be demonstrated as a predictor of trigeminal neuropathy. In the present study, we did not note a dose effect on cranial nerve neuropathy, probably because of the low prescription dose and narrow dose range. The incidence of facial nerve neuropathy was too low to allow statistical analysis.

A meta-analysis of hearing preservation after radiosurgery for vestibular schwannomas has been recently published in 2 articles including nearly 6000 patients.[6,7] A 57% preservation rate of serviceable hearing was reported.[6] Patient age and tumor size had no significant effect on hearing preservation, but radiation dose did matter.[6,7] In principle, this is in agreement with our study, although the method of hearing assessment was different. The original publications quoted by Yang and coworkers used either the Gardner and Robertson classification[16] or the classification of the American Association of Otolaryngology–Head and Neck Surgery.[6,7] Unlike these graded classification systems, we investigated serial pure tone audiometry, which yielded continuous data. However, upon applying the pure tone audiometry component of the Gardner and Robertson classification[16] to our data, we found a long-term serviceable hearing preservation rate of 75.1%, which was in agreement with the cited literature[4,6,7] and in particular fits well with the publication of Hansasuta and colleagues.[21] These authors used CyberKnife to treat vestibular schwannomas with total marginal doses of either 18 or 21 Gy using three 6- or 7-Gy fractions.[21] After a minimum 3-year follow-up, 74% of the patients with serviceable hearing[16] retained their ability at the last follow-up, and no patient with at least some hearing before treatment lost all hearing on the treated side.[21] The same result was achieved in our study, but with the single prescription dose of 12 to 13 Gy. In our study, a mean hearing loss of approximately 15–20 dB was found 5 years after radiosurgery. This suggests that ototoxicity of radiosurgery is low and little dependent on physical or technical parameters when modern treatment technology and adequate doses are applied. Further analysis of our data indicated that tumor recurrence was the main predictor of hearing loss in the treated ear; this correlation is a new finding and needs further confirmation by other investigators. In ambiguous clinical situations such as when a tumor increases in size after radiosurgery and it is unclear whether this reflects simply a swelling reaction or tumor recurrence, this new information may help in decision making.

We report on patients whom we treated over a 14-year span using 2 different treatment technologies. During these 2 eras, the indication for radiosurgery of vestibular schwannomas shifted toward a more proactive strategy; the treatment has been increasingly applied to smaller tumors, younger patients, and individuals with impaired, but not completely lost, hearing. The rate of deaf patients in the Gamma Knife period was higher compared with the CyberKnife period. The CyberKnife-treated patients were younger and their tumors were smaller than the Gamma Knife–treated individuals. These factors accounted for some weak statistical differences found by the univariate tests (Table 7). Multivariate regression models, however, did not confirm these differences in tumor control and toxicity

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Table 7. Comparison of outcome factors according to treatment technology

	Recurrence	NV Toxicity	NVII Toxicity	Ototoxicity
GK	16 (4.2%)	2 (0.5%)	5 (1.3%)	39 (24.4%)
CK	11 (2.9%)	6 (1.6%)	3 (0.8%)	18 (11.3%)
P	n.s.	0.02	n.s.	n.s.

Abbreviations: "recurrence," treatment failures; NV, trigeminal nerve; NVII, facial nerve; GK, Gamma Knife; CK, CyberKnife; *P*, significance in Fisher's exact test.

based on treatment technology. Furthermore, slight differences in dose prescription between the 2 technologies did not result in different outcomes. In summary, the results of the present study provide renewed support to the therapeutic concept of radiosurgery.[9,10] If appropriate technology and dose prescription are used, our study confirms radiosurgery to be a non-invasive and effective therapy for vestibular schwannoma with low relative toxicity.

Conclusion

Potentially significant clinical information has been generated during this study. First, following radiosurgical administration of a modern marginal single dose of 12–13 Gy, the most decisive factor for control of vestibular schwannoma is medical history of unrelated malignant tumor; second, tumor recurrence is predominantly predictive of hearing reduction after radiosurgery; and third, the concept of radiosurgery as defined by Lars Leksell[9,10] was effectively reproduced by 2 different treatment technologies with comparable outcomes.

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