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Treatment Outcomes and Dose Rate Effects Following Gamma Knife Stereotactic Radiosurgery for Vestibular Schwannomas

BACKGROUND: Gamma Knife radiosurgery (GKRS; Elekta AB) remains a well-established treatment modality for vestibular schwannomas. Despite highly effective tumor control, further research is needed toward optimizing long-term functional outcomes. Whereas dose-rate effects may impact post-treatment toxicities given tissue dose-response relationships, potential effects remain largely unexplored.

OBJECTIVE: To evaluate treatment outcomes and potential dose-rate effects following definitive GKRS for vestibular schwannomas.

METHODS: We retrospectively reviewed 419 patients treated at our institution between 1998 and 2015, characterizing baseline demographics, pretreatment symptoms, and GKRS parameters. The cohort was divided into 2 dose-rate groups based on the median value (2.675 Gy/min). Outcomes included clinical tumor control, radiographic progression-free survival, serviceable hearing preservation, hearing loss, and facial nerve dysfunction (FND). Prognostic factors were assessed using Cox regression.

RESULTS: The study cohort included 227 patients with available follow-up. Following GKRS 2-yr and 4-yr clinical tumor control rates were 98% (95% CI: 95.6%-100%) and 96% (95% CI: 91.4%-99.6%), respectively. Among 177 patients with available radiographic follow-up, 2-yr and 4-yr radiographic progression-free survival rates were 97% (95% CI: 94.0%-100.0%) and 88% (95% CI: 81.2%-95.0%). The serviceable hearing preservation rate was 72.2% among patients with baseline Gardner-Robertson class I/II hearing and post-treatment audiological evaluations. Most patients experienced effective relief from prior headaches (94.7%), tinnitus (83.7%), balance issues (62.7%), FND (90.0%), and trigeminal nerve dysfunction (79.2%), but not hearing loss (1.0%). Whereas GKRS provided effective tumor control independently of dose rate, GKRS patients exposed to lower dose rates experienced significantly better freedom from post-treatment hearing loss and FND ($P = .044$).

CONCLUSION: Whereas GKRS provides excellent tumor control and effective symptomatic relief for vestibular schwannomas, dose-rate effects may impact post-treatment functional outcomes. Further research remains warranted.

KEY WORDS: Vestibular schwannoma, Acoustic neuroma, Gamma Knife radiosurgery, Stereotactic radiosurgery, Neurosurgery, Radiation oncology, Dose rate

Vestibular schwannomas, also known as acoustic neuromas, are benign Schwann cell tumors of the skull base most commonly arising from the vestibular division of the vestibulocochlear nerve. Vestibular schwannomas represent approximately 11% of nonmalignant central nervous system tumors diagnosed in the United States, with an estimated

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ABBREVIATIONS: BED, biologically effective dose; **FND,** facial nerve dysfunction; **FSRT,** fractionated stereotactic radiotherapy; **GKRS,** Gamma Knife radiosurgery; **HA,** headache; **HL,** hearing loss; **LINAC,** linear accelerator; **PIV,** prescription isodose volume; **SRS,** stereotactic radiosurgery; **TTV,** treatment target volume; **TND,** trigeminal nerve dysfunction

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nationwide incidence of approximately 10 cases per million individuals per year.[1] Whereas vestibular schwannomas are benign tumors, potential risks when left untreated include permanent functional deficits, including hearing loss, tinnitus, dizziness, facial pain, numbness or paresthesias, and facial paralysis, as well as hydrocephalus and potentially life-threatening brainstem compression. Accordingly, treatment goals for vestibular schwannomas include local control, symptomatic relief, and effective preservation of existing neurological function while minimizing risks of potential harm (including, but not limited to, postoperative complications, treatment toxicities, and secondary malignancies).

Whereas ongoing surveillance remains appropriate for smaller and minimally symptomatic vestibular schwannomas, approximately 15%-40% of patients will develop local progression without treatment, potentially worsening permanent symptom burden and limiting available therapeutic options.[2-4] Whereas no prospective randomized trials have compared potential treatment approaches; both microsurgical resection and stereotactic radiation therapy are associated with excellent local control rates.[2] Nationwide, although microsurgery remains the most commonly used approach for vestibular schwannomas, stereotactic radiotherapy has become increasingly popular during recent years as a generally well-tolerated and noninvasive alternative.[5-8]

Definitive treatment options for vestibular schwannomas involving stereotactic radiotherapy include Gamma Knife radiosurgery (GKRS; Elekta AB), proton beam therapy, and linear accelerator (LINAC)-based treatments using stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT). Whereas retrospective data suggest excellent tumor control rates across modalities,[2,9,10] modern studies have not systematically compared radiotherapeutic treatment approaches beyond retrospective comparisons of LINAC-based SRS and FSRT. However, compared with surgical resection, stereotactic radiotherapy has been associated with both improved short-term hearing preservation rates[9] and higher patient-reported post-treatment quality of life.[11]

The Gamma Knife represents a particularly well-established treatment modality for vestibular schwannomas, backed by almost 50 years of documented clinical experience.[12-14] Compared with LINAC-based approaches, GKRS provides unparalleled treatment precision for intracranial tumors.[15] During the modern era, GKRS has demonstrated exceptional tumor control rates toward definitive treatment of vestibular schwannomas ranging from approximately 87% to 98%.[16-25] But whereas stereotactic radiotherapy maximizes likelihood of short-term hearing preservation compared with microsurgical resection, long-term hearing preservation rates remain lower than desired across treatment approaches, highlighting the importance of continued research toward optimizing current treatment paradigms.[9,10]

Notably, compared with other forms of external beam radiotherapy, GKRS (Elekta) operates using an alternative mechanism. Specifically, the Gamma Knife delivers radiation using spontaneously emitting radioactive cobalt-60 sources with a half-life of approximately 5.26 years, a measure that reflects the speed of radioactive decay (specifically describing the average time until decay of 50% of radioactive isotopes within given sources). Practically, because of this spontaneous decay, the actual rate of how quickly fixed radiation doses are delivered during GKRS varies across the lifespan of cobalt sources. In radiobiology, dose rate describes the rate of radiation dose delivery, defined as the amount of radiation absorbed by tissues per unit time. Theoretically, lower dose rates allow for more efficient repair of accumulated sublethal DNA damage within both tumors and surrounding normal tissues, which could potentially impact both tumor control and risks for late treatment toxicities. Because the Gamma Knife (Elekta) requires periodic replacement of cobalt-60 sources because of gradual radioactive decay, treatment dose rates during GKRS vary substantially depending on source age. Despite in vitro radiobiological evidence describing dose-rate effects, few studies have evaluated clinical implications of dose rate on treatment outcomes following GKRS. Interestingly, however, research suggests that dose-rate effects may impact both success and durability of pain relief following functional GKRS for trigeminal neuralgia using high prescription doses.[26] Based on fundamental differences in dose-response relationships between early- and late-responding tissues,[27] we hypothesized that dose-rate effects might impact local control and late toxicity rates following GKRS. For this reason, the purpose of this study was to evaluate both efficacy and potential dose-rate effects on clinical outcomes following definitive GKRS for vestibular schwannomas.

METHODS

Study Design

Experimental protocol and informed consent for this study were approved by our Institutional Review Board. This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for retrospective cohort studies. We retrospectively reviewed all patients from our medical center who underwent single-fraction radiosurgery using the Leksell Gamma Knife (Elekta) for unilateral vestibular schwannomas between April 1998 and April 2015. During this time, approximately 701 patients underwent definitive treatment for vestibular schwannomas, among whom, 419 (59.8%) received GKRS. Treatment recommendations were performed according to established institutional practices.[28] Briefly, GKRS was recommended for smaller and minimally symptomatic tumors (most commonly, for tumors measuring <2.2 cm in maximal diameter[14]) depending on patient preference, whereas microsurgical resection was recommended for patients presenting with debilitating pretreatment symptoms, larger tumors (typically, maximal diameter >3 cm), or mass effect on surrounding structures. Patients were treated using the Gamma Knife Model B (Elekta) before April 2011 and the Gamma Knife Perfexion system (Elekta) beginning in April 2011. On treatment day, patients underwent application of a Leksell G stereotactic head frame after administration of local anesthetic for immobilization under conscious sedation. Pretreatment volumetric magnetic resonance imaging sequences included 1-mm, axial, T1-weighted, contrast-enhanced images, 1- to 1.5-mm, axial, T2-weighted volume

images, and 3-mm, T2, whole-head imaging. Median prescribed SRS dose was 12.0 Gy (range: 11.0-16.8 Gy) to the 50% isodose line. The mean cochlear dose was 4 Gy. GKRS prescription doses above 12 Gy were used only for patients without pretreatment serviceable hearing according to institutional practice. Post-treatment follow-up assessments were performed at approximately 3 to 6 months intervals.

We collected baseline patient demographics (including age, gender, laterality, and pretreatment tumor size according to both maximum diameter and tumor volume; pretreatment tumor grade based on the Samii Classification system,[29] and pretreatment symptoms including hearing loss, tinnitus, dizziness, vertigo or disequilibrium, lateralized headache, facial nerve dysfunction [FND], and trigeminal nerve dysfunction [TND]) and dosimetric characteristics (including prescription isodose, maximum, minimum, and mean target doses, prescription isodose volume [PIV], treatment target volume [TTV]), RTOG conformity, selectivity, and homogeneity indices (conformity index, selectivity index, and homogeneity index, respectively)[30] and energy index, a proposed measure for target dose homogeneity independent of tumor volume and prescription dose.[31] Exclusion criteria included prior surgical resection (60 patients) and lack of available post-treatment follow-up information (118 patients). Given our interest in dose-rate effects, we identified 227 patients who were treated using a consistent GKRS prescription dose of 12 Gy to minimize potential confounding impacts on treatment outcomes. For evaluating clinical dose-rate effects, we divided the study cohort into 2 groups based on the median value for treatment dose rate, 2.675 Gy/min (range: 1.35-3.73 Gy/min). Pretreatment audiometric data were available for 157 patients (69%). Radiographic follow-up was available for 177 patients (78%).

Statistical Analyses

Patient characteristics, treatment parameters, and post-treatment symptomatic outcomes were characterized using descriptive statistics. Clinical and radiographic follow-up durations were determined using the reverse Kaplan-Meier method.[32] Radiographic progression was defined as persistently increased maximal tumor diameter by at least 2 mm at 3 years following completion of GKRS. Outcomes examined included clinical tumor control (defined based on freedom from salvage therapy following definitive GKRS), radiographic tumor control (defined based on time from GKRS until development of either asymptomatic or symptomatic radiographic progression), serviceable hearing preservation (defined as maintenance of Gardner-Robertson class I or II hearing for patients with available post-treatment audiometric information), symptomatic hearing preservation (defined based on freedom from patient-reported new or worsened hearing loss), and facial nerve preservation (defined based on freedom from either new or worsened FND). Additional symptomatic outcomes analyzed included lateralized headache, tinnitus, vertigo/dizziness/disequilibrium, TND, and secondary malignancies. Tumor control rates were determined using the Kaplan-Meier product limit method.[32] Survival curves were also generated using the Kaplan-Meier method,[32] evaluating survival differences between groups using Mantel-Cox log-rank tests. Univariable and multivariable logistic regression and Cox proportional hazards models were used to characterize post-treatment outcomes. Univariable regressions were performed with a threshold P value $< .2$ to identify potential covariates for multivariable analyses, which were performed using forward conditional modeling. P values $< .05$ were considered statistically significant without adjustment for multiple comparisons. Data analysis was performed using SPSS Statistics, Version 24 (IBM Corp., Armonk, New York).

TABLE 1. Patient Characteristics		
Baseline characteristics (227 patients)	**Value (%)**	**Range (IQR)**
Age (yr), median	60	27-91 (52-69)
Gender		
Male	111 (48.9%)	
Female	116 (51.1%)	
Laterality		
Left	116 (51.1%)	
Right	111 (48.9%)	
Symptomatic presentation		
Hearing loss	206 (90.7%)	—
Tinnitus	128 (56.4%)	—
Dizziness, vertigo, or disequilibrium	139 (61.2%)	—
Facial nerve (CN VII) dysfunction	9 (4.0%)	—
Trigeminal nerve (CN V) dysfunction	25 (11%)	—
Lateralized headache	21 (9.3%)	—
Tumor size		
Volume (cm³), median	0.43	0.01-9.00 (0.16-1.30)
Maximal diameter (cm), median	1.30	0.12-3.60 (0.90-1.70)
<1 cm	56 (26.4%)	
1-2 cm	139 (65.6%)	
>2 cm	17 (8.0%)	
Tumor stage (Samii Classification*)		
T1	84 (37.7%)	
T2	41 (18.4%)	
T3a	44 (19.7%)	
T3b	14 (6.3%)	
T4a	39 (17.5%)	
T4b	1 (0.4%)	
Pre-GKRS audiometry (n = 157)		
Gardner-Robertson class		
I	81 (51.6%)	—
II	26 (16.6%)	—
III, IV, or V	50 (31.8%)	—
Speech discrimination, %, mean (SD)	68.5% (34.8)	0%-100% [44-96]
PTA, mean (SD)	37.4 dB (22.4)	2-115 dB [20-52]
SRT, mean (SD)	33.0 dB (22.8)	0-105 dB [15-50]

*T1: intracanalicular; T2: extending beyond IAC; T3a: occupying cerebellopontine angle; T3b: occupying CPA; contacting brainstem without compression; T4a: brainstem compression; T4b: severe brainstem displacement and/or deformation of fourth ventricle.

RESULTS

Participants and Descriptive Data

Among 227 patients within the study cohort (Table 1), median pretreatment maximal tumor diameter was 1.3 cm (interquartile range (IQR): 0.90-1.70 cm). Before GKRS

TABLE 2. GKRS Treatment Parameters

GKRS treatment parameters	Value ± SD	Range (IQR)
Prescribed dose (Gy)	12	N/A
Prescription isodose (%), median	50	40-90 (50-50)
Mean target dose (Gy)	17.4 ± 4.3	12.9-70.2 (16.1-18.2)
Maximum target dose (Gy)	23.5 ± 6.4	13.3-100.6 (24.0-24.4)
Minimum target dose (Gy)	9.4 ± 3.0	2.7-39.8 (8.3-10.5)
Prescription isodose volume/PIV (cm³), median	0.68	0.01-9.20 (0.31-1.95)
Treated target volume/TTV (cm³), median	0.39	0.01-5.90 (0.15-1.19)
Dose rate (Gy/min), median	2.675	1.35-3.73 (2.05-3.13)
Energy index, median	1.42	0-2 (1.32-1.52)
Homogeneity index, median	0.48	0.15-2.24 (0.48-0.49)
Conformity index, median	1.88	0.94-4.48 (1.43-2.26)
Selectivity index, median	0.54	0.22-3.43 (0.44-0.69)

(Elekta AB), most patients were symptomatic from local tumor burden with most common pretreatment symptoms including hearing loss (90.7%), tinnitus (56.4%), and vertigo, dizziness, or disequilibrium (61.2%). Among 157 patients with available pretreatment audiological evaluations, 68.2% presented with baseline serviceable hearing defined as Gardner-Robertson class I or II functional status (Table 1). All patients underwent GKRS using a prescription dose of 12 Gy most commonly delivered to the 50% isodose line (Table 2). Median durations of clinical and radiographic follow-up were approximately 29.8 months (95% CI: 25.6-34.0 mo) and 29.4 mo (95% CI: 21.6-37.1 mo), respectively.

Outcomes

Following GKRS, 2-yr and 4-yr rates of clinical tumor control were approximately 98% (95% CI: 95.6%-100%) and 96% (95% CI: 91.4%-99.6%), respectively (**Figure, Supplemental Digital Content 1**). Patients benefited from a mean duration of freedom from salvage therapy lasting approximately 12.9 years (95% CI: 12.4-13.3 years). Radiographic progression-free survival rates were approximately 97% (95% CI: 94.0%-100.0%) at 2 years and 88% (95% CI: 81.2%-95.0%) at 4 years, respectively (**Figure, Supplemental Digital Content 2**) with a mean radiographic progression-free survival of 10.5 years (95% CI: 9.3-11.6 years). Among patients who initially presented with pretreatment serviceable hearing, the serviceable hearing preservation rate was 72.2%. Univariable and multivariable Cox regression analyses identified no factors that were significantly associated with clinical tumor control (Table 3), radiographic progression-free survival (Table 4) or serviceable hearing preservation (**Table, Supplemental Digital Content 3**). Two patients (0.9%) were diagnosed with secondary malignancies after a median duration of 4.4 years, although we identified no factors that were significantly associated with development of secondary malignancies (**Table, Supplemental Digital Content 4**).

Patient-reported functional outcomes are provided in Table 5. Encouragingly, after GKRS, most patients experienced effective symptomatic relief from many pretreatment symptoms including lateralized headache (94.7%), tinnitus (83.7%), balance problems (62.7%), FND (90.0%), and TND (79.2%), but not existing hearing loss (1.0%). Overall, 23.8% of patients with functionally intact pretreatment hearing developed new persistent hearing loss, and 24.2% of patients with symptomatic pretreatment hearing loss experienced symptomatic worsening.

Given our interest in potential dose-rate effects, we specifically evaluated whether dose rate was associated with treatment outcomes following GKRS. Overall, both clinical tumor control (Figure 1A) and radiographic tumor control (Figure 1B) rates were similar between the lower and higher dose-rate groups (logrank $P = .300$ and log-rank $P = .575$, respectively). Dose rate was also not significantly associated with either progressive hearing loss or progressive FND when evaluated as separate functional outcomes (**Table, Supplemental Digital Content 5** and **Table, Supplemental Digital Content 6**, respectively). Interestingly, however, GKRS patients exposed to lower treatment dose rates (< 2.675 Gy/min) experienced significantly better post-treatment survival free from both progressive symptomatic hearing loss and FND ($P = .044$) (Figure 1C). Multivariable Cox regression confirmed that GKRS exposure to treatment dose rates above 2.675 Gy/min was associated with increased risk of developing progressive post-treatment hearing loss, FND, or both (HR: 2.248, 95% CI: 1.082-4.672; $P = .030$) (Table 6), whereas larger pretreatment maximal tumor diameter appeared protective (HR: 0.324, 0.155-0.887, $P = .003$).

DISCUSSION

Key Results

Consistent with previous large cohort studies from the modern era,[16-25] we found that single-fraction GKRS (Elekta) provided excellent rates of clinical and radiographic tumor control as a definitive treatment modality for vestibular schwannomas. Alongside existing data from other large retrospective studies, these findings provide further support for definitive GKRS as a noninvasive treatment option for smaller vestibular schwannomas, providing durable tumor control with good functional outcomes. Encouragingly, whereas microsurgical resection was initially recommended for patients who presented with debilitating pretreatment symptoms, we found that most patients who underwent GKRS for mildly to moderately symptomatic vestibular schwannomas experienced effective symptomatic relief from prior tinnitus (83.7%), vertigo, dizziness and disequilibrium (62.7%), FND (90.0%), TND (79.2%), and lateralized headache (94.7%) following GKRS, but not existing hearing loss (1.0%). Despite limited availability of post-treatment audiological assessments, GKRS was also associated with a 72.2% serviceable hearing preservation rate within this cohort, consistent with prior estimates ranging from 34% to 86% across varying durations of follow-up,[18,21-23,25,33-49] Interestingly, we also

TABLE 3. Univariable and Multivariable Cox Regression for Clinical Progression-Free Survival Following Definitive GKRS for Vestibular Schwannomas

Covariate	Univariable regression		Multivariable regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.024 (0.946-1.109)	.560	—	
Gender				
Male	Reference	—	—	
Female	4.596 (0.513-41.185)	.173	—	.134 (NS)
Laterality				
Left	Reference	—	—	
Right	0.558 (0.093-3.346)	.523	—	
Year of diagnosis	0.940 (0.741-1.192)	.608		
Pretreatment serviceable hearing				
Yes (Gardner-Robertson I or II)	Reference	—	—	
No (Gardner-Robertson III, IV, or V)	2.139 (0.133-34.280)	.591	—	
Pretreatment hearing loss				
Yes	0.437 (0.049-3.908)	.459	—	
No	Reference		—	
Pretreatment CN VII dysfunction				
Yes	$0.045\ (0.000\text{-}6.7 \times 10^6)$	.713	—	
No	Reference		—	
Pretreatment CN V dysfunction				
Yes	$0.042\ (0.000\text{-}9.4 \times 10^3)$	.613	—	
No	Reference		—	
Tumor size, max. diameter	2.065 (0.414-10.307)	.377	—	
Tumor size, volume	0.805 (0.210-3.091)	.752	—	
Tumor grade (Samii classification)	1.110 (0.626-1.970)	.721	—	
Dose rate, median				
<2.675 Gy/min	Reference		—	
≥2.675 Gy/min	2.522 (0.413-15.394)	.316	—	
Dose rate, continuous	3.634 (0.782-16.886)	.100	—	.084 (NS)
Prescription isodose	0.923 (0.772-1.104)	.381	—	
Mean target dose (Gy)	1.046 (0.906-1.208)	.539	—	
Minimum target dose (Gy)	1.073 (0.830-1.387)	.591	—	
Maximum target dose (Gy)	1.033 (0.941-1.134)	.491	—	
RTOG conformity index	1.219 (0.215-6.897)	.823	—	
Paddick conformity index	$0.667\ (0.000\text{-}2.4 \times 10^3)$	.925	—	
Selectivity index	$0.627\ (0.000\text{-}1.3 \times 10^3)$	.905	—	
Energy index	$26.245\ (0.112\text{-}6.1 \times 10^3)$	.240	—	
RTOG homogeneity index	4.867 (0.147-161.6)	.376	—	

observed that vestibular schwannoma patients exposed to lower GKRS treatment dose rates (below 2.675 Gy/min) experienced significantly improved freedom from progressive symptomatic hearing loss and FND following treatment. Collectively, whereas GKRS provided excellent rates of both clinical and radiographic tumor control without evidence of potential dose-rate effects, our results suggest that dose-rate effects might impact cumulative risks for post-treatment toxicities following single-fraction GKRS.

Interpretation

According to classic radiobiology, dose-rate effects play an important role in determining the resulting biologic effects of a given absorbed dose of radiation. Lower dose-rate exposure might result in lower biologically effective doses (BEDs) within both tumor and surrounding normal tissues, which could poten-

tially impact both tumor control and post-treatment toxicities. Whereas dose-rate effects are well-documented in vitro, potential dose-rate effects are much more difficult to evaluate systematically in clinical practice. Practically, evaluating potential effects of treatment dose rate can be difficult given that patients undergoing GKRS in the setting of malignant tumors often have limited life expectancies, complicating routine assessment of late toxicities. Patients receiving GKRS for malignant tumors are also often receiving concurrent systemic treatments (including hormonal, chemotherapeutic, and immunotherapeutic agents), which also modulate local tissue responses and thereby complicate evaluation of radiation-induced treatment toxicities. For these reasons, vestibular schwannomas and other benign intracranial tumors represent an especially appropriate and relevant clinical context for evaluation of potential impacts of dose-rate effects on

TABLE 4. Univariable and Multivariable Cox Regression for Radiographic Progression-Free Survival Following Definitive GKRS for Vestibular Schwannomas

Covariate	Univariable regression		Multivariable regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.010 (0.970-1.052)	.634	N/A	
Gender				
Male	Reference	—	N/A	
Female	1.478 (0.593-3.682)	.401	N/A	
Laterality				
Left	Reference	—	N/A	
Right	1.036 (0.415-2.583)	.940	N/A	
Year of diagnosis	1.009 (0.885-1.150)	.896	N/A	
Pretreatment serviceable hearing				
Yes (Gardner-Robertson I or II)	Reference	—	N/A	
No (Gardner-Robertson III, IV, or V)	1.003 (0.311-3.234)	.997	N/A	
Pretreatment hearing loss				
Yes	1.026 (0.231-4.563)	.973	N/A	
No	Reference			
Pretreatment CN VII dysfunction				
Yes	0.044 (0.000-97.313)	.426	N/A	
No	Reference			
Pretreatment CN V dysfunction				
Yes	1.266 (0.289-5.548)	.754	N/A	
No	Reference			
Tumor size, max. diameter	0.623 (0.253-1.533)	.303	N/A	
Tumor size, volume	0.790 (0.381-1.635)	.525	N/A	
Tumor grade (Samii classification)	1.069 (0.801-1.427)	.651	N/A	
Dose rate, median				
< 2.675 Gy/min	Reference			
≥ 2.675 Gy/min	1.300 (0.518-3.265)	.576	N/A	
Dose rate, continuous	1.424 (0.716-2.834)	.314	N/A	
Prescription isodose	0.998 (0.953-1.045)	.926	N/A	
Mean target dose (Gy)	1.001 (0.912-1.097)	.991	N/A	
Minimum target dose (Gy)	0.950 (0.762-1.184)	.646	N/A	
Maximum target dose (Gy)	0.991 (0.913-1.076)	.838	N/A	
RTOG conformity index	0.908 (0.277-2.983)	.874	N/A	
Paddick conformity index	3.279 (0.023-469.685)	.639	N/A	
Selectivity index	3.416 (0.031-377.991)	.609	N/A	
Energy index	9.072 (0.317-259.60)	.198	N/A	
RTOG homogeneity index	0.748 (0.036-15.373)	.850	N/A	

long-term functional outcomes following GKRS. Whereas GKRS remains an extremely precise treatment modality, providing highly selective dose distributions while minimizing incident radiation exposure within surrounding normal tissue, late toxicities remain an important concern.

Current evidence suggests that dose-rate effects may influence treatment outcomes following brachytherapy for genitourinary and gynecologic tumors.[50-54] However, potential dose-rate effects on treatment outcomes following GKRS remain largely uncharacterized. Several studies have evaluated potential impacts of dose-rate effects on treatment outcomes following high-dose functional GKRS for trigeminal neuralgia,[26,55,56] with one study suggesting that higher dose-rate exposure might be associated with reduced short-term post-treatment pain intensity and reduced risk of

recurrent pain. Whereas potential dose-rate effects on post-treatment toxicities following GKRS remain unknown, anecdotal reports suggest that treatment toxicities may be more common after radioactive source changes. Accordingly, dosimetric analyses for functional GKRS have demonstrated that predicted biologically effective doses for a given prescription dose vary widely across the lifespan of radioactive cobalt-60 sources.[57]

Theoretically, lower dose rates might reduce late toxicity rates through better preservation of surrounding normal tissues by allowing for more effective sublethal DNA damage repair during treatment. However, lower dose rates could also potentially compromise tumor control by facilitating increased repair of sublethal radiation-induced tumor damage within tumor tissue. Classically, dose-rate effects are considered most relevant within

TABLE 5. Symptomatic Outcomes Following Definitive GKRS for Vestibular Schwannomas
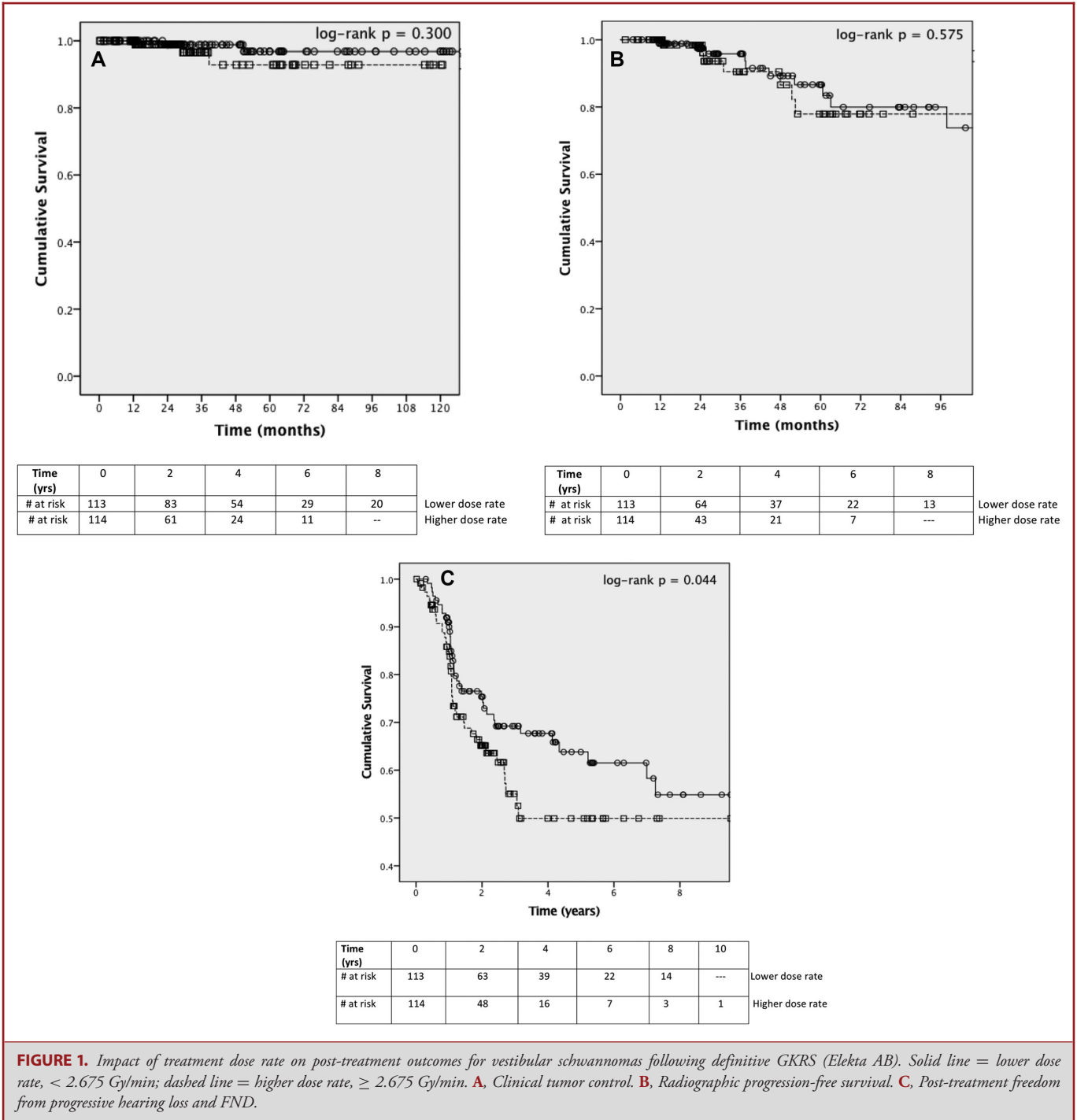
Post-treatment Symptoms	% (Frequency): Transient symptoms	% (Frequency): Persistent symptoms	% (Frequency): Total symptoms (Persistent or transient)
Hearing loss (HL)			
New-onset HL	14.3% (3/21)	23.8% (5/21)	38.1% (8/21)
Worsening of prior HL	3.9% (8/206)	50/206 (24.2%)	28.2% (58/206)
Improvement of prior HL	—	—	1.0% (2/206)
FND			
New-onset FND	4.6% (10/217)	4.1% (9/217)	8.8% (19/217)
Worsening of prior FND	0.0% (0/10)	0.0% (0/10)	0.0% (0/10)
Improvement of prior FND	—	—	90% (9/10)
TND			
New-onset TND	2.5% (5/203)	4.4% (9/203)	6.9% (14/203)
Worsening of prior TND	(0.0%) 0/24	4.2% (1/24)	4.2% (1/24)
Improvement of prior TND	—	—	79.2% (19/24)
Vertigo/dizziness/disequilibrium (V/D/D)			
New-onset V/D/D	10.8% (10/93)	16.1% (15/93)	26.9% (25/93)
Worsening of prior V/D/D	6.0% (8/134)	6.0% (8/134)	11.9% (16/134)
Improvement of prior V/D/D	—	—	62.7% (84/134)
Tinnitus			
New-onset tinnitus	1.9% (2/104)	5.8% (6/104)	7.7% (8/104)
Worsening of prior tinnitus	0.8% (1/123)	5.7% (7/123)	6.5% (8/123)
Improvement of prior tinnitus	—	—	83.7% (103/123)
Lateralized headache (HA)			
New-onset HA	1.0% (2/208)	2.4% (5/208)	7/208 (3.4%)
Worsening of prior HA	0.0% (0/19)	0.0% (0/19)	0/19 (0.0%)
Improvement of prior HA	—	—	18/19 (94.7%)

the approximate range of 0.1 Gy/hr to 10 Gy/min.[27] Whereas relevance of the traditional linear-quadratic model for SRS remains controversial,[58,59] late-responding tissues might theoretically derive most benefit from fractionation of treatment regimens toward reducing late treatment toxicities.[60]

Excitingly, the Gamma Knife Icon (Elekta AB, Stockholm, Sweden) offers new possibilities for alternative treatment paradigms using fractionated GKRS by facilitating highly reproducible fractionated SRS through a combination of frameless thermoplastic mask-based immobilization, integrated cone-beam computed tomography imaging, and real-time high-definition motion management monitoring. Interestingly, retrospective data have suggested that fractionated SRS may be associated with improved functional hearing preservation rates compared with single-fraction GKRS.[61] Prior dosimetric analyses evaluating hypofractionated SRS have also demonstrated exceptional treatment precision with the Gamma Knife (Elekta) compared with other modalities.[15] Encouragingly, preliminary data evaluating fractionated GKRS on the Gamma Knife Perfexion (Elekta) using a relocatable immobilization system appears promising.[62] Overall, fractionated GKRS represents a promising new approach for benign intracranial tumors toward potentially minimizing risks of late toxicities by combining the exceptional treatment precision of GKRS with the theoretical radiobiological advantages of treatment fractionation.

Limitations

Although these findings are interesting, important limitations should be considered given our retrospective study design, including, but not limited to, inherent selection biases associated with nonrandomized treatment assignments and attrition biases reflecting differential losses of patients to follow-up over time. Additional limitations include the lack of post-treatment audiometric reports for most patients within this cohort (limiting statistical power for detection of predictive factors for serviceable hearing preservation) and shorter than desired clinical and radiographic follow-up durations. We also acknowledge the fact that we did not control for potential effects of Gamma Knife model on study outcomes as an important limitation, given our institutional practice change during the study period. Regarding statistical analyses, we also did not perform adjustment for multiple comparisons, which also represents a noteworthy limitation given increased chance for potential false positives. Although intriguing that GKRS dose rate correlated with post-treatment freedom from progressive symptomatic toxicities, it is important to note that calibrated dose rates may not reflect actual in vivo dose rates within target volumes and surrounding tissues. Even within individual treatment plans, absorbed dose rates may vary tremendously given variations in 3-dimensional treatment volumes and patient anatomy. Moreover, even given a constant prescription dose and calibration dose rate, varying treatment times might still

FIGURE 1. *Impact of treatment dose rate on post-treatment outcomes for vestibular schwannomas following definitive GKRS (Elekta AB). Solid line = lower dose rate, < 2.675 Gy/min; dashed line = higher dose rate, ≥ 2.675 Gy/min.* **A**, *Clinical tumor control.* **B**, *Radiographic progression-free survival.* **C**, *Post-treatment freedom from progressive hearing loss and FND.*

impact dose rate effects.[63,64] Finally, it is important to note that GKRS treatment dose rate was not significantly associated with post-treatment freedom from progressive symptomatic hearing loss and progressive FND when analyzed as a continuous variable. Given that fact, along with the fact that rates of hearing loss and

FND were not significantly associated with dose-rate group when analyzed as separate variables, effect sizes may be fairly small. For all of these reasons, further research remains needed toward clarifying potential impacts of dose-rate effect on both individual and cumulative post-treatment toxicity rates following GKRS.

TABLE 6. Univariable and Multivariable Cox Regression for Post-treatment Freedom from Progressive Symptomatic Hearing Loss and FND following GKRS

Covariate	Univariable regression		Multivariable regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	0.995 (0.977-1.014)	.613	—	
Gender				
Male	Reference	—	—	
Female	1.085 (0.696-1.691)	.718	—	
Laterality				
Left	Reference	—	—	
Right	0.820 (0.527-1.278)	.381	—	
Year of diagnosis	1.027 (0.974-1.084)	.325		
Pretreatment serviceable hearing				
Yes (Gardner-Robertson I or II)	2.187 (1.098-4.356)	.026*	—	
No (Gardner-Robertson III, IV, or V)	Reference	—	—	.247 (NS)
Pretreatment hearing loss				
Yes	0.805 (0.402-1.613)	.541	—	
No	Reference		—	
Pretreatment CN VII dysfunction				
Yes	0.228 (0.032-1.641)	.142	—	.412 (NS)
No	Reference		—	
Pretreatment CN V dysfunction				
Yes	0.893 (0.429-1.857)	.761	—	
No	Reference		—	
Tumor size, max. diameter	0.407 (0.254-0.651)	.000*	0.324 (0.155-0.677)	**.003**
Tumor size, volume	0.633 (0.404-0.994)	.047*	—	.889 (NS)
Tumor grade (Samii classification)	0.753 (0.630-0.898)	.002*	—	.242 (NS)
Post-treatment tumor size				
Decreased	Reference	—	—	.554 (NS)
Stable	2.126 (1.084-4.169)	.028*	—	
Increased	2.619 (1.250-5.487)	.011*	—	
Dose rate, median				
<2.675 Gy/min	Reference		Reference	
≥2.675 Gy/min	1.581 (1.008-2.479)	.046*	2.248 (1.082-4.672)	**.030**
Dose rate, continuous	1.145 (0.820-1.600)	.427	—	
Prescription isodose	0.997 (0.976-1.019)	.800	—	
Mean target dose (Gy)	1.003 (0.961-1.047)	.881	—	
Minimum target dose (Gy)	0.953 (0.862-1.053)	.341	—	
Maximum target dose (Gy)	0.998 (0.966-1.031)	.905	—	
RTOG conformity index	1.292 (0.795-2.101)	.302	—	
Paddick conformity index	0.310 (0.034-2.866)	.302	—	
Selectivity index	0.334 (0.041-2.706)	.304	—	
Energy index	1.902 (0.540-6.697)	.317	—	
RTOG homogeneity index	1.004 (0.300-3.353)	.995	—	

CONCLUSION

Despite these limitations, our findings provide further support for the efficacy of GKRS (Elekta AB) as a definitive treatment modality for vestibular schwannomas, whereas highlighting important questions in the field of radiosurgery regarding potential toxicities. Indeed, whereas single-fraction GKRS provides excellent local control rates for vestibular schwannomas and remains a longstanding and well-validated treatment approach, our findings highlight the importance of further research concerning potential dose-rate effects on long-term functional outcomes after GKRS. Indeed, whereas single-fraction GKRS remains an excellent treatment option for vestibular schwannomas and other benign intracranial tumors, future research combined with technologic advances such as the Gamma Knife Icon (Elekta) will be essential toward further optimization of long-term functional outcomes.

Disclosures

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Supplemental Digital Content 1. Figure. Clinical tumor control for vestibular schwannomas after definitive GKRS.

Supplemental Digital Content 2. Figure. Radiographic progression-free survival for vestibular schwannomas after definitive GKRS.

Supplemental Digital Content 3. Table. Univariable and multivariable regression examining Gardner-Robertson serviceable hearing preservation after definitive GKRS.

Supplemental Digital Content 4. Table. Univariable and multivariable regression examining post-treatment secondary malignancies after definitive GKRS.

Supplemental Digital Content 5. Table. Univariable and multivariable Cox regression for post-treatment freedom from progressive symptomatic hearing loss following GKRS.

Supplemental Digital Content 6. Table. Univariable and multivariable Cox regression for post-treatment freedom from progressive FND following GKRS.