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The Relevance of Biologically Effective Dose for Hearing Preservation After Stereotactic Radiosurgery for Vestibular Schwannomas: A Retrospective Longitudinal Study

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BACKGROUND: Stereotactic radiosurgery has become a common treatment approach for small-to-medium size vestibular schwannomas.

OBJECTIVE: To evaluate relationship between time (beam-on and treatment) and risk of hearing decline after stereotactic radiosurgery for vestibular schwannomas in patients with Gardner–Robertson (GR) baseline classes I and II.

METHODS: This retrospective longitudinal single-center study included 213 patients with GR I and II treated between June 2010 and December 2019. Risk of passing from GR classes I and II (coded 0) to other classes III, IV, and V (coded 1) and the increase in pure tone average (continuous outcome) were evaluated using a mixed-effect regression model. Biologically effective dose (BED) was further assessed for an alpha/beta ratio of 2.47 ($Gy_{2.47}$).

RESULTS: Binary outcome analysis revealed sex, dose rate, integral dose, time [beam-on time odds ratio 1.03, $P = .03$, 95% CI 1.00-1.06; treatment time ($P = .02$) and BED ($P = .001$) as relevant. Fitted multivariable model included the sex, dose rate, and BED. Pure tone average analysis revealed age, integral dose received by tumor, isocenter number, time (beam-on time odds ratio 0.20, $P = .001$, 95% CI 0.083-0.33) and BED ($P = .005$) as relevant.

CONCLUSION: Our analysis showed that risk of hearing decline was associated with male sex, higher radiation dose rate (cutoff 2.5 Gy/minute), higher integral dose received by the tumor, higher beam-on time ≥20 minutes, and lower BED. A BED between 55 and 61 was considered as optimal for hearing preservation.

KEY WORDS: Biologically effective dose, Treatment time, Irradiation time, Gamma Knife, Vestibular schwannoma, Hearing, Radiosurgery, Stereotactic radiosurgery

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ABBREVIATIONS: BED, biologically effective dose; **GK,** gamma knife; **GR,** Gardner–Robertson; **IAM,** internal acoustic meatus; **PTA,** pure tone average; **RDR,** radiation dose rate; **SRS,** stereotactic radiosurgery; **VS,** vestibular schwannomas.

Vestibular schwannomas (VSs) represent approximately 8% of all intracranial tumors and the most common cerebellopontine angle neoplasm in adults.[1] They arise from the vestibular division of the eighth cranial nerve, particularly from

myelinating Schwann cells that surround their neurons.[2] The common use of contrast-enhanced MRI account for an increased observe incidence during the past 3 decades.[3] The most usual symptom at detection remains ipsilateral sensorineural hearing decline,[4] followed in case of tumor growth by various signs of cranial nerve, brainstem, and/or cerebellum compression.[1]

Currently, there is no high-level evidence[5] (lowest among all intracranial neoplasms)[6] suggesting what is the best management approach,[7] including "wait-and-scan" strategy, microsurgical resection, or stereotactic radiosurgery (SRS). Treatment option depends upon clinical presentation, tumor size, and the expertise of the treating center.[6] Recent studies suggested that larger initial tumor size and faster growth rates were associated with an elevated risk of loss of serviceable hearing.[8] During the past decades, SRS has become one of the most routine approaches for VSs. Among benign tumors, SRS for VSs has the largest body of evidence, particularly with regards to tumor control, hearing preservation, and cranial nerve outcomes in general.[9-12]

With regards to SRS, physical dose prescription has been considered the gold standard treatment approach for the past 6 decades. For VSs, there has been a dose de-escalation during time,[10] which had led to similar tumor control, while decreasing the risk of facial palsy to less than 1% in modern series and increasing the probability of hearing preservation.[10,11,13] Recently, it has been suggested that factor time in which a physical dose is delivered might be more relevant with regards to outcomes.[14]

Here, we hypothesized that irradiation time and biologically effective dose (BED, initially developed by Barendsen[15,16] and further by Fowler[17]) would play a role in hearing preservation after SRS for VS. We sought to investigate this in a homogenous series in which a large majority of cases have been treated with a marginal uniform physical dose of 12 Gy.

METHODS

Type of Study

This is a single-center retrospective, longitudinal study. Lausanne University Hospital Ethical Committee was requested for this study by the ENT group (number 2020-01989) as part of a larger vestibular schwannoma clinical research analysis, in collaboration with the ENT department. Patients provided written informed consent for the procedure.

Patient Population

Patients (n = 213, consecutive) with useful baseline hearing (Gardner–Robertson [GR] baseline class I and II) treated as first intention with SRS, independently of Koos grade, in Lausanne University Hospital between June 2010 (establishment of our radioneurosurgery center) and December 2019 are part of the present analysis. We excluded patients with type II neurofibromatosis, already treated with radiation (independently of the technique), previously operated, or patients with intracochlear and/or intravestibular tumors.

The mean follow-up clinical and neuroimaging period in this cohort was 39 months (median 36 months, range 6-84 months). A minimum of 2, 3, and 5 years of follow-up was obtained in 165, 127, and 82 cases, respectively. The number of cases with 10 years of follow-up was small and thus excluded from the present analysis. Basic demographic data can be found in Table 1.

TABLE 1. Basic Demographic Data

Variable	n, % or mean, SD (range)
Age, years	Mean 52.2, median 54 (21.7-86.1)
Sex	
Male	104 (48.4%)
Female	111 (51.6%)
Side	
Left	109 (50.7%)
Right	106 (49.3%)
Symptom at discovery	
Tinnitus	25 (11.6%)
Incidental	24 (11.2%)
Hearing loss	124 (57.7%)
Vertigo	42 (19.5%)
Koos grade at baseline	
I	65 (30.2%)
II	75 (34.9%)
III	72 (33.5%)
IV	3 (1.4%)
VS maximal diameter	13.2 ± 5.6 (2.5-29.5)
Baseline hearing (GR class)	
1	154 (71.6%)
2	59 (28.4%)
PTA	
Baseline	32.9 ± 14.4 (3.7-66.2)
6 mo after GK	38.7 ± 18.7 (2.5-110)
12 mo after GK	42.2 ± 18.6 (2.5-130)
36 mo after GK	44.4 ± 19.2 (2.5-97.5)
60 mo after GK	47.1 ± 18.5 (5-95)

GK, gamma knife; GR, Gardner–Robertson; PTA, pure tone average; VS, vestibular schwannomas.

Preoperative Assessment

All patients benefitted from standard clinical and neuroimaging assessment. Particularly, audiological evaluation was made using the GR class,[18] including both speech discrimination score and pure tone average (PTA). Serviceable hearing was defined as GR class I and II, with a speech discrimination score higher than 50% and a PTA less than 30 dB. The detailed

TABLE 2. Dosimetric Data

Variable	Mean, SD (range)
Target volume (mL)	0.9 ± 1.3 (0.005-7.8)
Prescription isodose volume (mL)	1.1 ± 1.4 (0.015-8.5)
Physical dose (marginal dose, Gy)	12 Gy in 210 (97.7%) cases; 11 Gy in 5 (2.3%) cases
Coverage (%)	98.5 ± 1.3 (93.8-100)
Gradient index (units)	3.1 ± 0.7 (2.2-7.9)
Paddick index	0.74 ± 0.1 (0.28-1.42)
Radiation dose rate (Gy/min)	2.8 ± 0.6 (1.7-3.8)
Cochlea (dose max, Gy)	4.2 ± 1.4 (1.5-10.4)
Cochlea (dose mean, Gy)	2.9 ± 0.83 (0.6-6.6)
Number of isocenters (units):	
Corresponding to the tumor	8.9 ± 7.1 (1-32)
Corresponding to the internal acoustic meatus	Mean 2.5, median 2 (1-9)
Time (min)	
Beam-on time	36.3 ± 18.1 (7.3-101.8)
Treatment time	38.8 ± 18.5 (9-106)
Treatment time minus couch-in and couch-out	37.9 ± 18 (8.9-102.8)
Couch-in and couch-out (together)	0.9 ± 0.7 (0.1-3.2)
Beam-on time corresponding to isocenters in the IAM	16.9 ± 8.9 (2.44-56.2)
Integral dose	
VS (tumor)	14.7 ± 21 (0.1-116.7)
IAM (all volume)	2 ± 1 (0.6-6.3)
IAM (corresponding only to primary beams)	1.6 ± 1 (0.6-3)
BED tumour ($Gy_{2.47}$)	57.1 ± 4.5 (42.7-66.3)

BED, biologically effective dose; IAM, internal acoustic meatus; VS, vestibular schwannomas.

GR I and II class, as well as the PTA at baseline and during follow-up can be found in Table 2. The House and Brackmann[19] grading system was used for evaluating the facial nerve function. We also evaluated other cranial nerve functions, particularly the trigeminal nerve. Koos classification was used to assess the relationship between the tumor and the surrounding structures.[20]

Postoperative Assessment

Postoperative assessment was performed at 6, 12, 24, 36, 60, and 84 months after SRS using otoneurological outpatients' tests, brain MRI, and neurosurgery consultation.

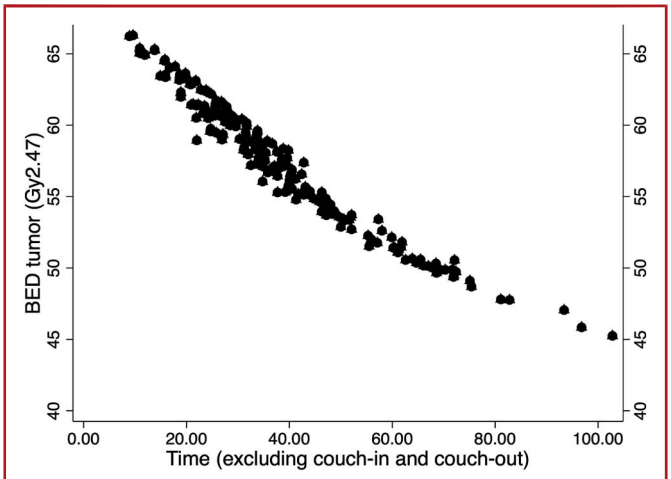

FIGURE 1. *Correlation between time factor and BED calculation. BED, biologically effective dose.*

Radiosurgical Technique

All patients were treated using the Leksell Gamma Knife Perfexion (Elekta Instruments, AB, up to June 2016) and ICON (up-to-date). After application of Leksell stereotactic model G frame under local anesthesia, we always perform stereotactic MRI and computer tomography for the target and organ at risk definition. The MRI sequences include T1- and T2-weighted constructed interference in steady-state/fast imaging using steady-state acquisition (Fiesta) sequences, both with and without contrast enhancement.[21] As per previous studies, special attention has been given to the dose received by the cochlea, particularly in patients with functional hearing.[22,23] We used, whenever necessary, beam channel blocking, to keep the maximal dose to the cochlea below 5.2 Gy (whenever possible), as previously reported in the literrature.[24] Mean maximal dose received by the cochlea in the present series was 4.2 ± 1.4 (1.5-10.4) Gy.

We standardly prescribe 12 Gy as marginal physical dose, in agreement with dose de-escalation studies already published by Kondziolka et al[10] In the present series, only 5 (2.3%) patients received 11 Gy, the rest being treated with 12 Gy.

For this study, we particularly noted the number of isocenters within the internal acoustic meatus (IAM) and the beam-on time corresponding to such isocenters (by performing the sum of the time duration for those isocenters related to the IAM). Moreover, we have individually drawn the IAM and calculated the integral dose received by this structure and by the tumor. Also, we have drawn the part in the IAM where the primary beams were located and further calculated the integral dose received by such.

The dosimetric data can be found in Table 2.

Time Factor (Beam-On and Treatment Time)

Of note, no unscheduled time gaps were noted within the individual treatments.

The mean beam-on time was 36.3 ± 18.1 minutes (range 7.3-101.8). The mean treatment time was 38.8 ± 18.5 (range 9-106). The details can be found in Table 2.

Radiation Dose Rate

The mean radiation dose rate was 2.8 ± 0.6 (1.7-3.8) Gy/minute.

TABLE 3. Random-Effect Logistic Regression Model (Univariable and Multivariable Analysis) for the Gardner–Robertson Class 1 and 2 (Coded 0) vs Class 3, 4, or 5 (Coded 1)

Variable	Odds ratio	*P* value	95% CI
Univariate analysis			
Sex	4.14	.01	1.32; 12.92
Dose rate	3.13	.02	1.18; 8.30
Integral dose received by the IAM	1.20	.51	0.68; 2.11
Integral dose received by the tumor	1.02	.03	1.00; 1.05
Maximal dose received by the cochlea	1.10	.66	0.71; 1.70
Mean dose received by the cochlea	0.98	.91	0.73; 1.30
Number of isocenters	1.06	.114	0.98; 1.14
Number of isocenters with impact to the IAM	0.92	.7	0.59; 1.42
Koos grade (reference Koos I)			
II	2.66	.18	0.61; 11.49
III	4.23	.05	0.99; 18.06
IV	146.76	.01	3.08; 6986.97
BED tumour ($Gy_{2.47}$)	0.93	.001	0.902; 0.974
Time			
Beam-on time	1.03	.03	1.00; 1.06
Treatment time	1.03	.03	1.00; 1.06
Treatment time minus (couch-in and couch-out)	1.03	.03	1.00; 1.06
Multivariate analysis			
Hearing at 36 mo	4.47	.008	1.46; 13.63
Hearing at 60 mo	12.04	<.0001	3.48; 41.67
Sex	6.69	.01	1.47; 30.32
Dose rate	6.62	.005	1.78; 24.62
BED tumor ($Gy_{2.47}$)	0.82	.01	0.69; 0.96

BED, biologically effective dose; IAM, internal acoustic meatus.

Primary Aim

The primary outcome was to correlate changes in hearing class (quantified as the risk of passing from GR class I and II to classes III, IV, and V or changes in PTA as continuous values) and the time factor (beam-on time and treatment time).

Biologically Effective Dose Calculation

To account for the time effect caused by repair of sublethal damage, BED was calculated using the approach originally developed by Fowler.[25] Such concepts have been later theoretically discussed for SRS by Jones and Hopewell.[26] Alpha/beta ratio was considered 2.47. We acknowledge, however, such an alpha/beta is usually assigned for normal brain[27]; as for VSs, it has been considered as ranging between 1.8 and 3[28-32] or even up to 4 Gy.[31] Couch-in and couch-out, in which there is no opening of the cobalt sources, were excluded from total time calculation. Thus, we considered the beam-on time, from which we derived the treatment time, as being ($n \times t + (n - 1) \times 0.1$ minutes), n being the number of isocenters and t is the isocenter treatment duration.

The mean BED was 57.1 ± 4.5 (42.7-66.3) $Gy_{2.47}$ (Figure 1).

Statistical Analysis

Statistical analysis was performed using Stata 16.1 (StataCorp. 2019, Stata Statistical Software: Release 16: StataCorp LLC). Descriptive statistics were related as proportion/frequency for categorical data, and mean, median, and range for continuous variables. The risk of hearing decline was assessed using 2 outcomes. The first (binary outcome) was to consider a decline from GR class I and II (coded 0) to GR III, IV, or V (coded 1). The second was to evaluate the PTA as a continuous value (continuous

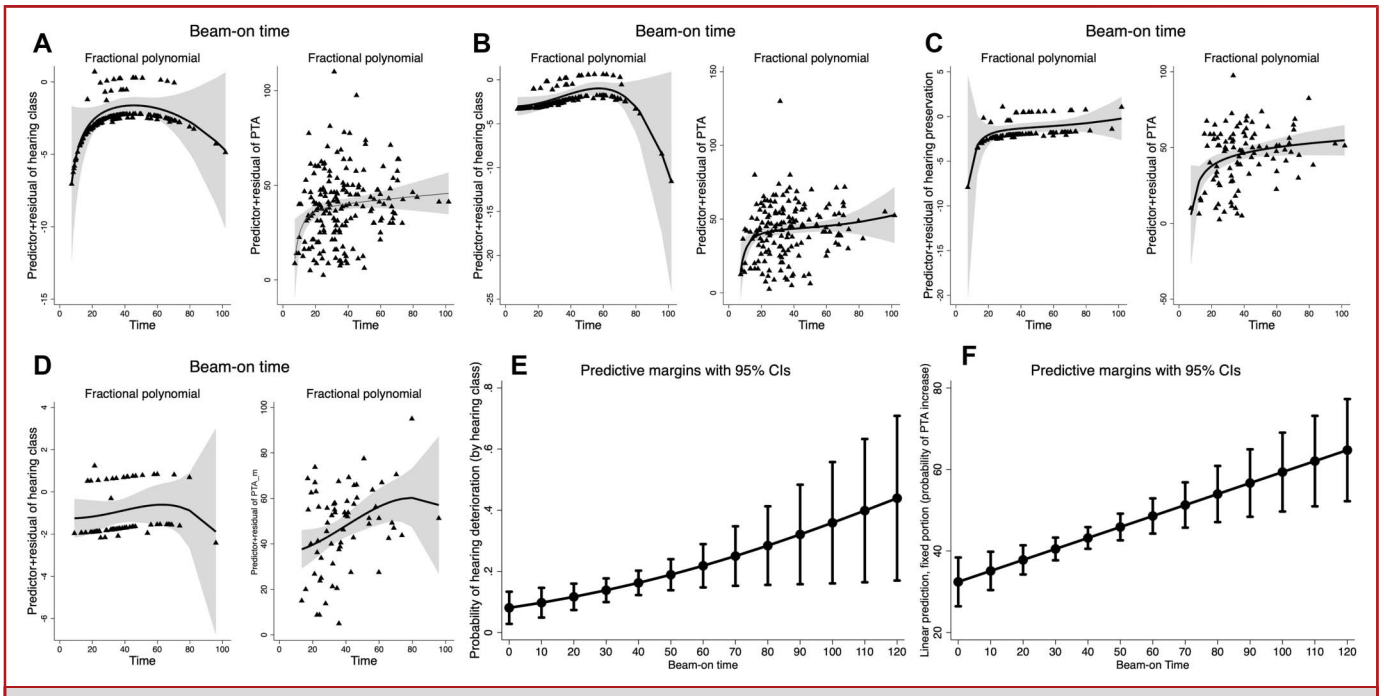

FIGURE 2. *Probability of hearing decrease after Gamma Knife radiosurgery as correlated with beam-on time at different time points after SRS:* **A**, *at 6 months,* **B**, *at 12 months,* **C**, *at 36 months,* **D**, *at 60 months after SRS;* **E**, *overall prediction of hearing decrease (by Gardner–Robertson class, as correlated with beam-on time); and* **F**, *overall prediction of hearing decrease probability by continuous PTA values. PTA, pure tone average; SRS, stereotactic radiosurgery.*

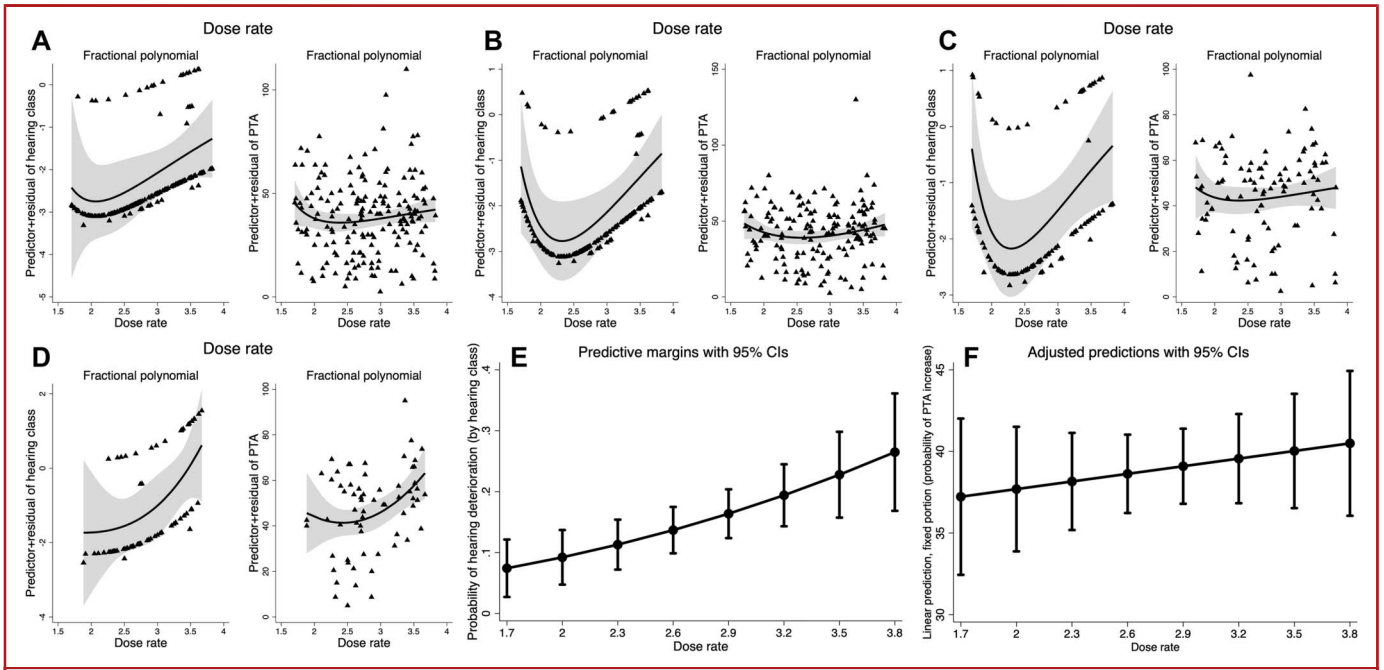

FIGURE 3. *Probability of hearing decrease after Gamma Knife radiosurgery as correlated with radiation dose rate time at different time points after SRS:* **A**, *at 6 months,* **B**, *at 12 months,* **C**, *at 36 months,* **D**, *at 60 months after SRS;* **E**, *overall prediction of hearing decrease (by Gardner–Robertson class, as correlated with radiation dose rate); and* **F**, *overall prediction of hearing decrease probability by continuous PTA values. PTA, pure tone average; SRS, stereotactic radiosurgery.*

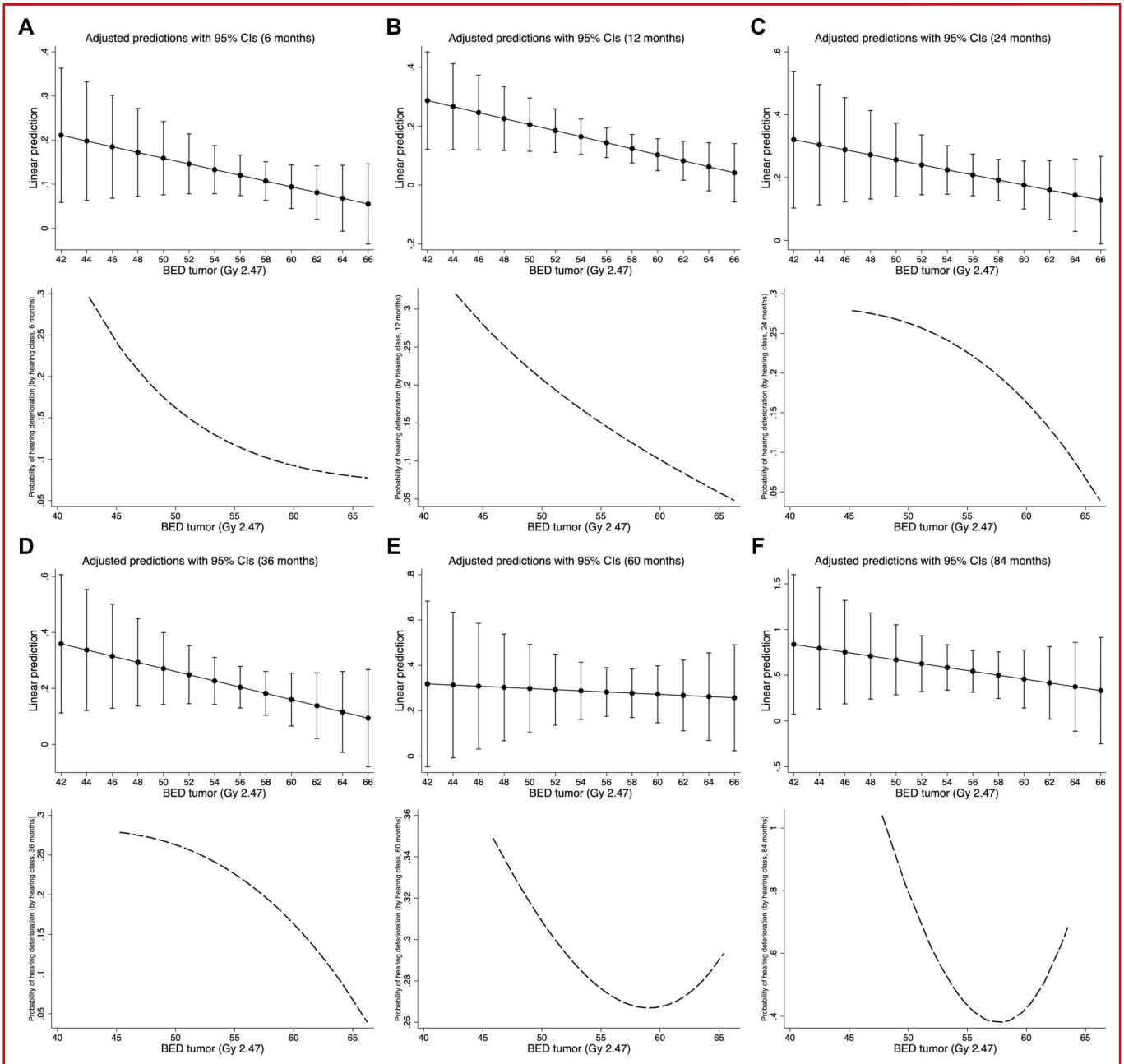

FIGURE 4. *BED as a predictor for hearing deterioration for different time points, as per Gardner–Robertson class, at* **A***, 6 months;* **B***, 12 months;* **C***, 24 months;* **D***, 36 months;* **E***, 60 months; and* **F***, 84 months after stereotactic radiosurgery; upper side: linear prediction; lower side: probability of hearing deterioration (by hearing class). BED, biologically effective dose.*

outcome). The binary outcome was analyzed using a random-effect logistic model, and the strength of the association with covariate was measured using the odds ratio (OR) and its calculated *P*-value. For the continuous outcome, we used a random-effect linear model, and the strength of the association with covariate was measured using the β coefficient and its calculated *P*-value. For both outcomes, significantly associated covariates with $P \leq .10$ were used in a backward procedure to fit a multivariable model.

RESULTS

Risk of Hearing Decline from GR Classes I and II to III, IV, or V (Binary Outcome, Table 3).

The univariable analysis revealed as relevant sex (male sex being a risk factor, OR 4.14, $P = .01$, 95% CI 1.32-12.92), radiation dose

TABLE 4. Random-Effect Linear Regression Model (Univariable and Multivariable Analysis) for the PTA (Continuous Outcome)

Variable	β	*P* value	95% CI
Univariate analysis			
Age	0.27	.003	0.089; 0.45
Integral dose received by the IAM	−0.93	.93	−1.36; 2.17
Integral dose received by the tumor	0.17	.002	0.067; 0.28
Number of isocenters	0.42	.006	0.12; 0.73
Mean dose received by the cochlea	0.54	.27	−0.43; 1.53
Dose rate	1.55	.42	−2.26; 5.37
BED tumor ($Gy_{2.47}$)	−0.67	.005	−1.15; −0.198
Time			
Beam-on time	0.20	.001	0.083; 0.33
Treatment time	0.20	.001	0.081; 0.32
Treatment time minus couch-in and couch-out	0.20	.001	0.084; 0.33
Multivariate analysis			
Hearing at 36 mo (baseline ref)	5.19	<.001	3.44; 6.94
Hearing at 60 mo	6.96	<.001	4.91; 9.01
Age	0.28	.008	0.074; 0.491
BED tumor ($Gy_{2.47}$)	−0.941	.001	−1.505; −0.376
Integral dose received by the IAM	2.42	.06	−0.172; 5.028

BED, biologically effective dose; IAM, internal acoustic meatus; PTA, pure tone average.

rate (RDR) (OR 3.13, *P* = .02, 95% CI 1.18-8.30), integral dose received by the tumor (OR 1.02, *P* = .03, 95% CI 1.00-1.05), Koos grade (reference Koos I, and for exemplification Koos III, OR 4.23, *P* = .05, 95% CI 0.99-18.06), time (beam-on time, OR 1.03, *P* = .03, 95% CI 1.00-1.06, treatment time, OR 1.03, *P* = .03, CI 1.00-1.06 and treatment time minus [couch-in plus couch-out] OR 1.03, *P* = .03, 95% CI 1.00-1.06; Figure 2A-2E; for hearing deterioration as by increasing of PTA function of time, please see Figure 2F). The OR of 1.03 implies a 3% hearing deterioration risk per minute; for 10 additional minutes, OR was 1.38, (risk of 38%) and for 20 minutes, 1.92 (92% risk, *P* < .001).

Were not statistically significant: maximal dose received by the cochlea (OR 1.1, *P* = .66, 95% CI 0.71-1.70), mean dose received by the cochlea (OR 0.98, *P* = .91, CI 0.73-1.30), integral dose delivered to the IAM (OR 0.77, *P* = .42, 95% CI 0.42-1.44), number of isocenters in the IAM (OR 0.92, *P* = .7, 95% CI 0.59-1.42), or irradiation time corresponding to isocenters within the IAM (OR 1.02, *P* = .44, 95% CI 0.96-1.09; Table 3).

Multivariate analysis revealed sex (OR 6.69, *P* = .01, 95% CI 1.47-30.32), dose rate (OR 6.62, *P* = .005, 95% CI 1.78-24.62; Figure 3A-3F), and tumor BED (OR 0.82; *P* = .01; CI 0.69-0.96). Corresponding receiver operating characteristic curve was of 0.6918 (*P* < .0001 for sex, dose rate, and $BED_{2.47}$).

BED was statistically significant (OR 0.93, *P* = .001, CI 0.902-0.974). Lower BED was associated with higher probability of hearing decline. An optimal BED for hearing preservation was considered between 55 and 61 (Figure 4A-4F).

Risk of Hearing Decline in Terms of Increasing of PTA (Continuous Outcome, Table 4).

The univariable analysis identified the following covariates as being significantly associated with the outcome in terms of increasing of PTA: age (beta coefficient 0.27, *P* = .003, 95% CI 0.089-0.45), integral dose received by the tumor (beta coefficient 0.17, *P* = .002, 95% CI 0.067-0.28), number of isocenters (beta coefficient 0.42, *P* = .006, 95% CI 0.12-0.73), and time [beam-on time beta coefficient 0.20, *P* = .001, 95% CI 0.083-0.33, treatment time beta coefficient 0.20, *P* = .001, 95% CI 0.081-0.32 and treatment time minus (couch-in plus couch-out) beta coefficient 0.20, *P* = .001, 95% CI 0.084-0.33; Figure 2F].

The following covariates were not statistically significant: the maximal dose received by the cochlea (beta coefficient 0.14, *P* = .87,

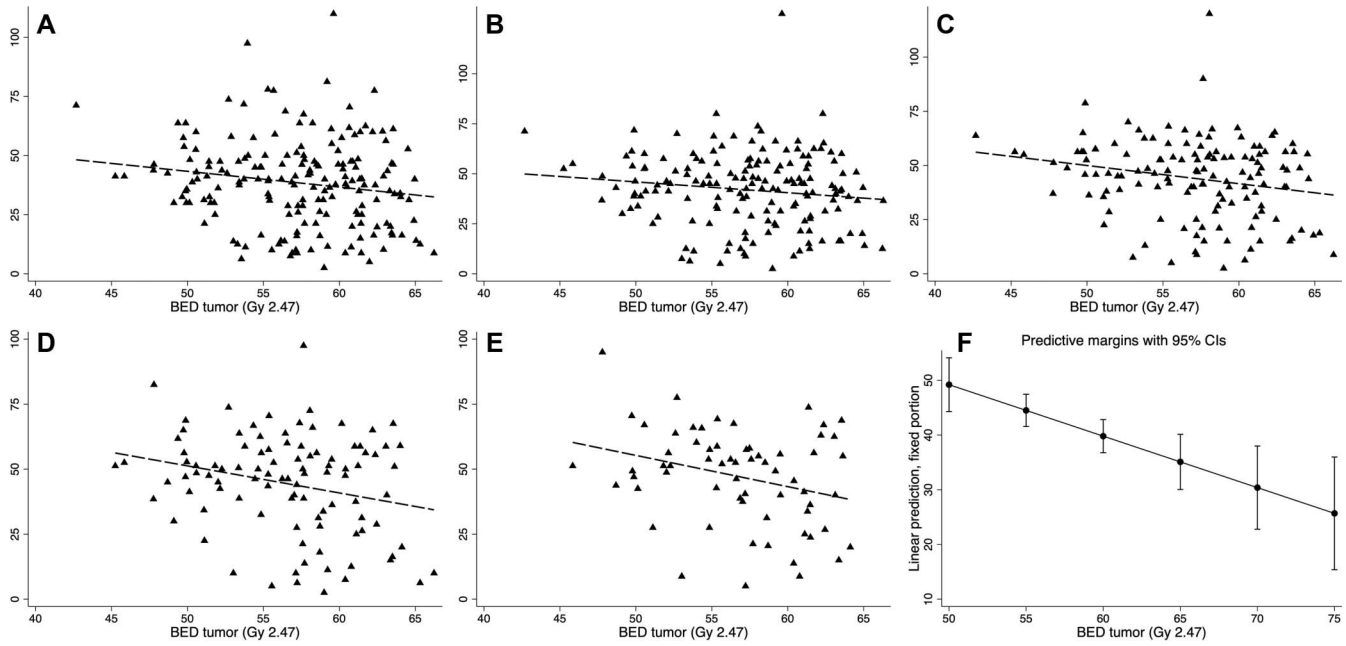

FIGURE 5. *BED as a predictor for hearing deterioration for different time points, as per continuous pure tone average values, at* **A**, *6 months;* **B**, *12 months;* **C**, *24 months;* **D**, *36 months; and* **E**, *60 months after stereotactic radiosurgery;* **F**, *overall linear prediction of hearing deterioration as function of BED delivered to the tumor. BED, biologically effective dose.*

95% CI −1.62 to 1.91), mean dose received by the cochlea (beta coefficient 0.54, $P = .27$, 95% CI −0.43 to 1.53), the integral dose delivered to the IAM (beta coefficient −0.93, $P = .93$, 95% CI −2.36 to 2.17), the number of isocenters in the IAM (beta coefficient −0.047, $P = .95$, 95% CI −1.80 to 1.70), or the irradiation time corresponding to isocenters within the IAM (beta coefficient 0.07, $P = .60$, 95% CI −0.19 to 0.34).

Tumor BED Was Statistically Significant (Beta Coefficient −0.67; $P = .005$; 95% CI −1.15 to [−0.198], Figure 5A-5)

The multivariable analysis identified age (beta 0.28, $P = .008$, 95% CI 0.074-0.491) and tumor BED (beta −0.94, $P = .001$, 95% CI −1.505 to −0.376) as statistically significant. There was a linear relationship between the PTA values and tumor BED (Figure 4).

Risk of Hearing Decline (Difference in PTA Between Follow-Up Time Point and Baseline, Continuous Outcome, Table 5, Figure 6)

The mean PTA loss at 6 months was 38.5 ± 18.6 dB (2.5-110), at 12 months was 41.9 dB ± 18.6 (2.5-130), at 24 months 44 dB ± 18.5 (2.5-120), at 36 months 44.4 dB ± 19.2 (2.5-97.5), at 60 months 47.1 dB ± 18.5 (5-95), and at 84 months was 58.5 dB ± 14 (38.5-71.25).

TABLE 5. Regression Model for the Difference in PTA (Follow-up—Baseline, Illustrated at 24, 36, and 60 Months, Continuous Value)

Variable	Odds ratio or β coefficient	*P* value	95% CI
Mean dose received by the cochlea	Odds ratio		
24 mo	2.6	.03	1.07; 6.32
36 mo	1.35	.69	0.300; 6.123
BED tumor ($Gy_{2.47}$)	β		
24 mo	−0.655	.009	−1.14; −0.17
36 mo	−0.700	.01	−1.24; −0.151
60 mo	−1.224	.003	−2.014; −0.435

BED, biologically effective dose; PTA, pure tone average.

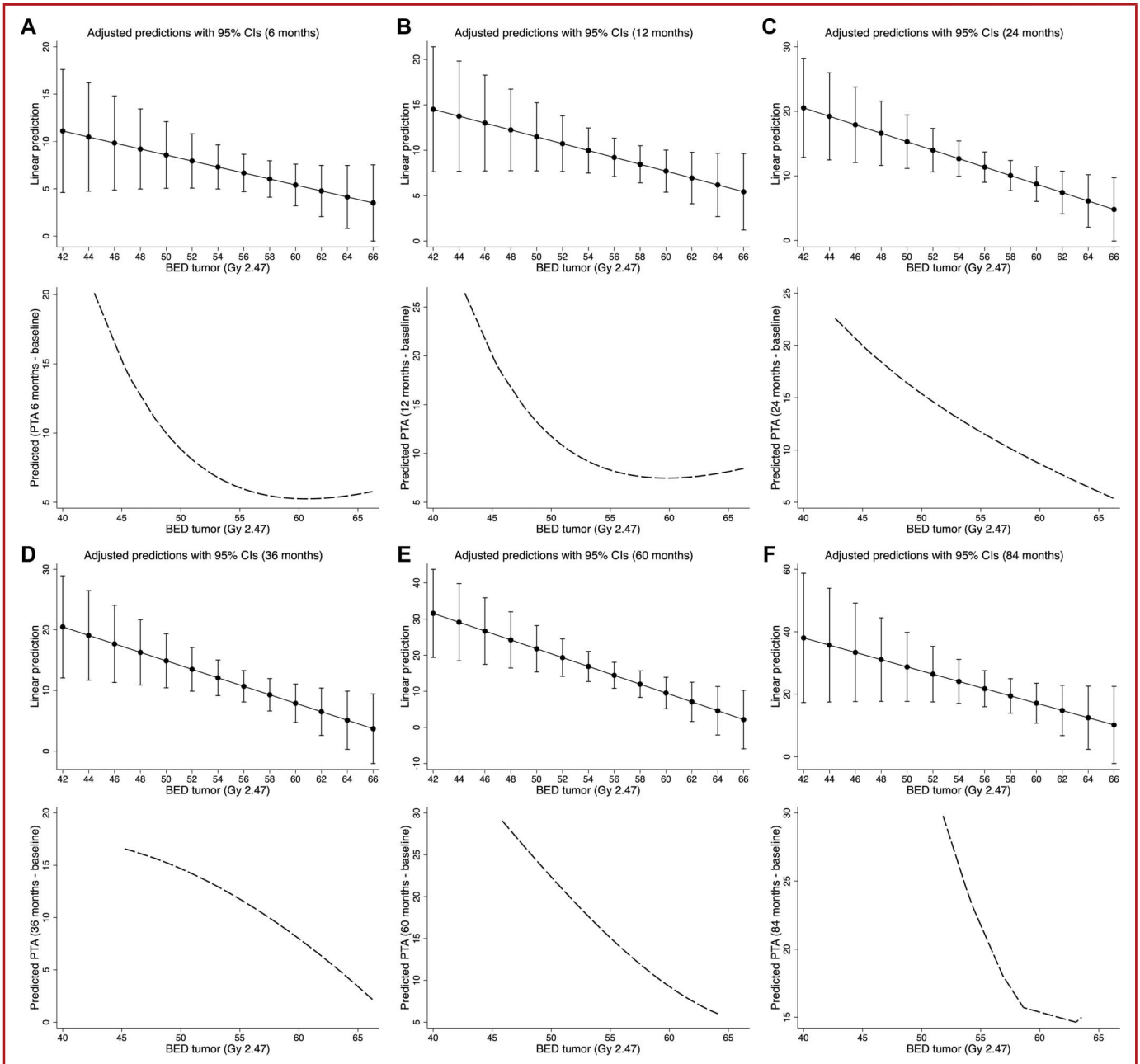

FIGURE 6. *BED as a predictor for hearing deterioration for different time points, as per continuous PTA values (follow-up minus baseline) at* **A***, 6 months;* **B***, 12 months;* **C***, 24 months;* **D***, 36 months;* **E***, 60 months; and* **F***, 84 months after stereotactic radiosurgery; upper side: linear prediction; lower side: predicted PTA loss. BED, biologically effective dose; PTA, pure tone average.*

The relationship between hearing deterioration in terms of PTA difference was statistically significant for tumor BED, at various time points, as illustrated in Table 5 and Figure 6A-6F. The mean dose received by the cochlea was statistically significant only at 24 months, but not for other time points.

DISCUSSION

In this study, we studied the effects of SRS on hearing preservation in terms of the effect of time (beam-on, treatment, and the difference between treatment time and couch-in plus couch-out in which no irradiation is performed) in which a physical dose

was delivered. Of note, a majority of this cohort (97.7% of patients) was treated with a uniform dose prescription of 12 Gy. Our most significant finding was the association between higher beam-on and treatment time (more than 20 minutes) and hearing decline, as well as between lower BED and hearing decline, as also recently suggested by Berger et al.[33] Particularly, a BED value between 55 and 61 was considered a good compromise for hearing preservation. In addition, our analysis showed that risk of hearing decline from GR classes I and II to III, IV, or V was associated with male sex, higher RDR (cutoff 2.5 Gy/minute), and higher integral dose received by the tumor. With regards to the risk of increase in PTA, such was associated with increase in age, integral dose received by tumor, as well as time factor (both beam-on and treatment time).

Our results suggest, for the first time, a major role played by the irradiation time and treatment time after SRS for VSs. Moreover, other findings are consistent with previous literature on several axes, already evaluated by other teams. Regarding the age, younger patients have higher probability of hearing preservation, which is in line with published data.[13,23,34,35] With respect to the integral dose received by the tumor, such has not been previously suggested as relevant for hearing preservation after SRS. However, in a previous study, Massager et al[22] found that higher integral dose received by the intracanalicular part of the VSs treated by SRS was associated with worse hearing prognosis.

The RDR has already been hypothesized to affect treatment outcomes after SRS. In a previous study, we suggested that lower RDR (less than 2.5 Gy/minute) is associated with a decreased risk of developing acute radiation effects.[24] Similar results were reproduced by Smith et al,[36] suggesting that lower RDR (less than 2.675 Gy/minute) was associated with less facial nerve dysfunction and freedom from symptomatic progressive hearing loss. However, after Smith et al[36] suggested a role of RDR in clinical outcomes, we advocated that the time factor and further the BED could be more relevant compared with the RDR in a letter underlying such aspects.[14]

A factor that was evaluated in this cohort was the different available options for what is considered the time, including the beam-on, treatment time, and a quantification of treatment time minus the couch-in plus couch-out (in which the cobalt-60 sources are closed and no irradiation is delivered). Of note, all were statistically significant with identical *P* values and almost identical odds ratios and 95% CIs. Such is explained by the fact that all patients have been treated with Leksell Gamma Knife Perfexion and ICON (Elekta Instruments, AB) and thus with automatized gamma knife (GK) models, and so the time frame between isocenters has dramatically decreased compared with former older GK models, being currently between 0.04 and 0.1 minutes. In this respect, the treatment time and the beam-on time are almost identical, explaining such results. We do consider that because of these statistically significant and almost identical results for different time calculations (beam-on, treatment etc), the couch-in and couch-out should be excluded from the definition of treatment time for GK models Perfexion and ICON, as they induce additional minutes, which are not to be considered.

An important aspect to keep irradiation time as low as possible might be related to inverse planning systems, such as Lightning (Elekta Instruments, AB).[37] Such systems allow to dramatically decrease the irradiation time, providing patients treated for VSs higher chances of hearing preservation, in the light of our findings.

Limitations

Our study has several inherent limitations, particularly related to retrospective analysis. Another limitation, in our view, is the choice of an alpha/beta ratio of 2.47 for this particular study. Classically, such value is considered for normal brain. However, in the absence of a golden standard and because of recent controversies in the literature, we decided to use 2.47 for this particular study.

CONCLUSION

The time factor in which a physical dose is delivered is, in our opinion, a core parameter that should be considered in the future of SRS treatment planning. Longer beam-on time (more than 20 minutes) is associated with worse hearing preservation rates (in terms of GR class). Lower BED values up to 5 years after SRS are associated with hearing decline. For hearing preservation, our data suggest an optimal BED value between 55 and 61. Inverse planning systems (Gamma Knife Lightning), which allow delivering shorter treatment times, would particularly help for VSs in keeping this parameter as low as possible, to be able to offer patients better hearing preservation rates. Radiobiological fingerprint of single-fraction SRS is at the beginning of what will potentially create a paradigm shift in the next decades.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors report potential additional features related to outcomes for VS SRS using the Gamma knife. They have concentrated on the dose rate at the time of SRS, which is dependent in part on the activity of the cobalt sources. Most centers report that tumor margin dose, isodose, maximum dose, tumor volume, margin conformality, selectivity (dose fall off outside the tumor margin) patient age, pre-SRS hearing status, and average (not maximum) cochlear dose are statistically related to useful hearing preservation (GR or AOA grades 1-2). The implication of the current study is that dose rate also affects the outcomes. From the scatter plots, curves are generated that suggest that higher dose rates (e.g. hotter cobalt sources) were associated with worse hearing outcomes. The authors suggest that contouring and inverse dose planning might be helpful to improve hearing outcomes, as in theory, it could use larger (thus faster) isocenters to treat at higher-margin isodoses and lower maximum doses, thereby reducing the beam on time. Actual published patient experience has shown the following features to be important: dose prescription, volume, isocenters used, blocking, conformality, selectivity (dose fall off), average cochlear dose, patient age, and length of time between diagnosis and SRS. If one ignored these features by concentrating on the dose rate, I suspect that the current clinical outcomes defined over the past 35 years will be adversely affected.

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