Usefull Hearing Preservation Is Improved in Vestibular Schwannoma Patients Who Undergo Stereotactic Radiosurgery Before Further Hearing Deterioration Ensures

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Abstract

Introduction

The present study evaluates whether hearing deterioration during observation reduces serviceable hearing preservation rates after stereotactic radiosurgery (SRS) in vestibular schwannoma (VS) patients with useful hearing.

Methods

We retrospectively analyzed 1447 VS patients who underwent SRS between 1992 to 2017. We identified 100 VS patients who had Grade I Gardner- Robertson (GR) hearing at initial diagnosis but were observed without surgery or SRS. We compared hearing after SRS in 67 patients who retained GR Grade I hearing from initial diagnosis to SRS (the hearing maintenance or HM group) to 33 patients whose hearing worsened from GR grade I to grade II (the hearing deterioration or HD group). We also investigated whether a decline in pure tone average (PTA) or speech discrimination score (SDS) before SRS affected hearing preservation after SRS.

Results

The serviceable hearing (GR I and II) preservation in HM patients was 80%s, 63%, and 51% at 3, 5, and 10 years, respectively. The serviceable hearing preservation in HD patients was 40%, 33%, and 20% at 3, 5, and 10 years, respectively. In multivariate analysis, younger age (<55 years, p=0.012) and HM during observation (p<0.001) improved serviceable hearing preservation rates. Patients whose PTA increased ≥15 dB (p=0.011) or whose SDS declined ≥10% (p=0.024) had reduced serviceable hearing preservation rates.

Conclusions

Hearing deterioration during observation before SRS reduced long term hearing preservation rate in VS patients with GR grade I hearing at initial diagnosis. SRS before hearing deterioration was recommended for hearing preservation.

Introduction

Vestibular schwannomas (VS) generally are slow-growing tumors that arise from the vestibular portion of the eighth cranial nerve. The most common presenting symptom is ipsilateral hearing loss[1]. The wide spread use of Magnetic Resonance Imaging (MRI) has led to earlier diagnosis of often smaller volume VS, so that some patients have remarkably good hearing at diagnosis[2, 3]. For such patients observation or “wait and scan” is often recommended[4]. For patients with symptomatic larger volume VSs, microsurgical resection remains a potent intervention[4]. Stereotactic radiosurgery (SRS) for VS was first reported in 1971 by Leksell[5]. SRS using the Leksell Gamm Knife (GK) (AB Elekta) for small to medium size VSs has a resection free rate of over 95% in 10 years with an associated transient facial neuropathy

rate of 1-5% and a serviceable hearing preservation rate of 43-68% at 5 years after SRS[6–9]. Early SRS after diagnosis improves hearing preservation[10, 11]. Based on referral patterns and wait and scan recommendations from initial consultants some patients with serviceable hearing were observed and underwent SRS only after hearing deterioration or tumor progression was recognized. The aim of this study was to evaluate whether hearing deterioration during observation of VS patients with GR grade I affected hearing preservation after SRS.

Methods

Patients population

We retrospectively analyzed 1447 VS patients who underwent GK SRS at our center between 1992 and 2017. Patients who underwent SRS before1992 received higher margin doses (18 Gy-20 Gy) and were excluded from this study. We also excluded patients who had undergone prior resection, prior radiation therapy, or who had neurofibromatosis type 2. We identified 100 VS patients who had Gardner-Robertson (GR) grade[12] I hearing at initial diagnosis and were then were observed. Serviceable hearing was defined as GR grade I and II (PTA $\leq$50 dB and SDS $\geq$50%). The flow diagram of this study population is shown in Fig.1. We compared long term hearing after SRS in 67 patients whose hearing remained GR grade I from initial diagnosis to SRS (hearing maintenance or HM group) with 33 patients whose hearing worsened from GR grade I to II at the time of SRS (hearing deterioration or HD group). We also evaluated whether hearing preservation was related to worsening PTA and SDS values during the observation. There were 64 males and 36 females. The median age was 55.2 years (range, 24-80 years). Seventy-seven patients had tinnitus before SRS, and 41 patients had vertigo symptoms before SRS. Prior to SRS, no patient had facial neuropathy, but two patients had trigeminal neuralgia, and 5 patients had trigeminal neuropathy. Twenty-eight patients were classified as Koos grade[13] I at SRS, 30 as grade II, 23 as grade III, and 19 as grade IV. The median interval between initial diagnosis and SRS was 17.4 months (range, 3.1-190.2 months). Median follow-up after SRS was 4.4 years (range, 0.5-21.0 years). The detailed patient characteristics are shown in Table 1. This study was approved by the University of Pittsburgh Institutional Review Board (IRB 0404192).

Radiosurgery Technique

SRS was performed in a single procedure that began with stereotactic head frame application using local anesthesia supplemented by intravenous conscious sedation. Patients then underwent high-definition MRI and/or CT imaging studies as appropriate. SRS was performed using various models of the Leksell Gamma knife R (Model U, B, C, 4C, Perfexion and Icon (Elekta AB)). Dose planning was performed using various versions of the Leksell dose planning software (KULA or Leksell Gammaplan)[6, 14]. Radiation was delivered in a single session with typical margin dose of 12-13 Gy delivered to the tumor margin. The median margin dose was 12.5 Gy (range, 11.5-15.0 Gy). The median maximum dose was 25.0 Gy (range, 13.6-30.0 Gy). Tumor volume was defined as the calculated volume enclosed in treatment marginal dose at the time of SRS. The median target tumor volume was 0.60 cm^3 (range, 0.06-11.0 cm^3).

Patient follow-up

After SRS, patients had imaging, hearing testing and clinical examination recommended at 0.5, 1, 2, 4, 8, 12, 16, 20 and 24 years. At any time when new symptoms were detected patients underwent a CT and/or MRI.

Statistical analysis

The data was analyzed using SPSS Statistics, version 25.0 (IBM, New York, USA). The relationship between HM and HD patients were analyzed statistically using Fischer's exact test and Mann-Whitney analysis as appropriate. Age, sex, tinnitus before SRS, SDS at diagnosis, target volume, margin dose, maximum dose, interval between diagnosis and SRS, and follow up time were not significantly different between these groups. We did find that HM patients reported less vertigo symptoms and had better PTA values than HD patients (Table 1). More HM patients had Koos grade I tumors compared to HD patients (Table 1). The detailed difference between HM and HD patients are shown in Table 1. Tumor enlargement after SRS was defined as a tumor volume that increased by ≥15%. Kaplan-Meier plots for tumor control rates were created. Hearing deterioration was defined as a decline from GR grade I or II (serviceable) to III-V (non-serviceable, SDS <50% or PTA >50 dB). Kaplan-Meier plots for hearing preservation rates were created starting at the date of SRS. Univariate analysis was performed on the Kaplan-Meier method using a log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. The suggested cutoff value for variables (age, PTA at diagnosis, SDS at diagnosis, target volume, margin dose, and interval between diagnosis and SRS) were determined by a Youden index based on receiver operating characteristic curve analysis[15]. P value of <0.05 were considered statistically significant.

Results

Tumor control

The tumor control rate after SRS was 98.9% at 3 years, 95.3% at 5 years, and 92.2% at 10 years. In univariate analysis, there was no significant difference in tumor control rates between HM and HD patients (p =0.535). Four patients had tumor progression during follow-up. Three patients were observed without additional treatment because the tumors had initial enlargement but then stabilized. These patients were one HD patient and two HM patients, but all three patients had hearing deterioration from 12 to 54 months after SRS. A single patient underwent additional SRS (margin dose 11.0 Gy) at 4.5 years after initial SRS. This patient was HM patient, maintained useful hearing, and had no complications at 23 months after repeat SRS.

Serviceable hearing preservation

At the last follow up, 42 of 67 HM patients maintained serviceable hearing, whereas 8 of 33 HD patients had preserved serviceable hearing. The detailed comparison of GR hearing at diagnosis, SRS, and last follow-up are shown in Table 2. The overall serviceable hearing preservation rate was 65.9% at 3 years,

52.5% at 5 years and 40.5% at 10 years (Fig. 2a). The serviceable hearing preservation rates of HM patients were 79.9% at 3 years, 63.4% at 5 years, and 51.2% at 10 years. In contrast the serviceable hearing preservation rates of HD patients were 40.0% at 3 years, 32.7% at 5 years, and 19.6% at 10 years (Fig. 2b). In univariate analysis, younger age (<55 years, p=0.006), better PTA at diagnosis (<20 dB, p=0.024), and HM status (p <0.001) were associated with improved long-term serviceable hearing preservation rates. The following factors were not significantly associated with serviceable hearing preservation rates: sex (p=0.119), tinnitus (p=0.643), vertigo symptoms (p=0.118), Koos grade (grade I & II vs. III & IV, p=0.882), SDS at diagnosis (<94% vs. ≥94%, p=0.603), target tumor volume (<0.6 cm^3 vs. ≥0.6 cm^3, p=0.510), margin dose (<13 Gy vs. ≥13 Gy, p=0.729), and observation interval (<2 years vs. ≥2 years, p=0.706). In multivariate analysis, younger age (<55 years, p=0.012, HR 2.21, 95% CI 1.19-4.11) and HM group (HM status, p <0.001, HR 2.85, 95% CI 1.68-5.41) were significantly associated with improved serviceable hearing preservation rates (Table 3).

Does deterioration of the PTA or SDS during observation affect hearing preservation after SRS?

During the observation interval (median interval 17.4 months) before SRS, the median PTA increased from 16.9 dB to 21.25 dB and the median SDS decreased from 96% to 92%. The median increase in PTA was 6.85 dB and the median decrease in SDS was 4%. In univariate analysis, patients with an increase in the PTA ≥15 dB during observation had reduced serviceable hearing preservation rates (p=0.024) (Fig. 2c). Similarly, patients whose SDS decreased ≥10% had reduced serviceable hearing preservation rates (p=0.024) (Fig. 2d). GR grade I HM patients whose PTA worsened by ≥6 dB had significantly reduced GR grade I maintenance (p=0.005) (Fig. 2e). Patients whose SDS decreased by ≥5% also had a reduced probability of maintaining GR grade I hearing (p=0.028) (Fig. 2f). Patients with a PTA at SRS of <20 dB (p=0.010) had a higher probability of maintaining GR grade I.

Facial and trigeminal neuropathy

In this series, 99% maintained House-Brackman[16] (HB) grade I facial nerve function after SRS. One patient developed mild facial neuropathy (HB grade III) at 20.7 months after SRS. The Margin dose of this patient was 12.5 Gy and the tumor volume remained stable. Three patients developed transient facial spasms 8 to 38 months after SRS. No patient developed trigeminal neuropathy (defined as decrease in sensation, new pain or new paresthesia within ipsilateral trigeminal nerve distribution after SRS) in this series.

Discussion

Current management options for newly diagnosed VSs include observation, SRS, and surgical resection[4, 17]. In prior decades before the wide availability of MRI for screening of patients with asymmetric hearing loss, tinnitus, or disequilibrium symptoms, many VS tumors were not detected until the tumor resulted in major cranial nerve or neurological dysfunction. For symptomatic larger tumors with brain stem compression early complete resection became the most frequent intervention in patients without

significant medical comorbidities. In patients with significant medical comorbidities subtotal resection followed by adjuvant SRS more recently has become an additional option[18–20]. In 1971, Leksell first reported the potential role of SRS for vestibular schwannomas (acoustic neuromas)[5]. In 1989, Kondziolka et al reported 162 consecutive VS patients who underwent Gamma knife SRS; they noted tumor control in 98% and unchanged hearing in 51% of patients [21]. In 2006, Pollock et al. reported a prospective cohort study comparing surgical resection with SRS for patients with small- to moderate-sized VS[22]. They described no difference in tumor control, and described excellent cranial nerve preservation rates. After these and many other SRS reports emerged, further observation of smaller tumors rather than early surgical intervention was increasingly recommended.

Further observation was based on the premise that VS tend to grow slowly, and in any case outcomes from intervention are not worsened during an observational interval after the first confirmatory MRI[23, 24]. The present report examines the question of whether even mild hearing deterioration during an initial observation (or “wait and scan”) interval leads to worse hearing outcomes in a series of patients who eventually proceed with SRS.

Prior Reported Hearing Results in SRS Patients

We reported that VS patients with serviceable hearing at the time of SRS had overall serviceable hearing preservation rates of 77.8% at 3 years, 68.8% at 5 years, and 51.8% at 10 years[14]. Akpinar et al. compared hearing outcomes in early SRS patients (≤2 years after diagnosis) with late SRS hearing outcomes (>2 years after SRS). This report confirmed that earlier SRS resulted in better hearing preservation outcomes[11].

In the present study we evaluated hearing outcomes in patients who had normal or GR Grade 1 hearing at the time of initial diagnosis. In this retrospective study some patients maintained GR 1 hearing during the observation interval until SRS was performed. We compared those patients to a similar group of patients whose hearing had worsened during the observation interval. The multivariate analysis revealed that those without hearing worsening (HM Patients) and those younger than 55 years had significantly better useful hearing preservation rates after SRS. We and others have previously reported the beneficial effect of younger age in hearing preservation results after SRS[9, 14]. The present study confirms that only those patients whose hearing does not worsen during observation have the best chance of long-term hearing preservation once SRS is performed. Patients whose hearing deteriorated during observation before SRS had worse hearing outcomes after SRS.

Regis et al. performed a study that evaluated intracanalicular VS patients who underwent early SRS or “wait and scan strategy” [10]. They found that tumor control and functional hearing preservation rates were higher in patients who underwent early SRS.

Many patients are now diagnosed by MRI performed for relatively mild or even non-specific symptoms such as asymmetric hearing loss, vague imbalance symptoms, vertigo, or tinnitus. If a small VS is found on MR, these patients are often referred to an otolaryngologist or neurosurgeon. After review of the

hearing results, they may recommend a period of observation with a new scan in 6 -12 months. Patients may be told their tumor is benign and grows slowly. Some patients delay subsequent imaging if the symptoms remain mild and non-progressive. Referral for intervention by either surgery or radiosurgery may not occur for months or even years.

What We Learned

Based on our experience in more than 2000 VS patients over a 32 year interval, we suspected that earlier SRS might lead to better hearing preservation rates- and that hearing maintenance is an important outcome measure for many VS patients. We found that both PTA and SDS measurements are important predictors of hearing outcomes during such an observation interval. VS patients whose PTA increased $\geq$6 dB or whose SDS decreased by $\geq$5% were less likely to retain GR grade I after SRS. Even more dramatic changes such as an PTA increase of $\geq$15 dB or a SDS decrease $\geq$10% during observation led to less serviceable hearing preservation. Of interest, Kirchman et al reported 10 years hearing outcomes in observed intracanalicular VS patients[25]. They found that the median PTA increased from 51 dB to 72 dB and median SDS decreased from 60% to 34% after follow-up of 9.5 years. In the current experience series, the median PTA increased from 16.9 dB to 21.3 dB at the time of SRS (median interval 17.4 months) and SDS decreased from 96% to 92%.

Study limitations

This is a retrospective study, and lacks data related to tumor volume changes during the interval between first diagnosis and SRS. The HM group and HD group were not matched for PTA at diagnosis, presence of vertigo before SRS, and Koos grade. This study found that even mild hearing deterioration during the observation period before SRS significantly reduced the ability to maintain useful hearing after SRS.

Conclusions

To improve the long term maintenance of serviceable hearing in VS patients with Grade 1 hearing at diagnosis, we advocate SRS before further hearing deterioration is detected.

Declarations

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Availability of data and material: All data pertaining to this research article are included within the manuscript as written.

Code availability: Not applicable to this work.

Authors` contributions

Conception and design: Hideyuki Kano, Akiyoshi Ogino. Acquisition of data: Akiyoshi Ogino, Hao Long, Stephen Johnson, Andrew Faramand. Analysis and interpretation of data: Akiyoshi Ogino. Drafting the article: Akiyoshi Ogino. Critically revising the article: Hideyuki Kano, L. Dade Lunsford. Reviewed submitted version of manuscript: All authors. Statistical analysis: Hideyuki Kano. Administrative/technical/material support: L. Dade Lunsford, John C. Flickinger. Study supervision: Hideyuki Kano, L. Dade Lunsford, John C. Flickinger.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: The authors affirm that human research participants provided informed consent for publication.

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Tables

Table 1. Characteristics of 100 patients with vestibular schwannoma

Characteristics	Total	HM group	HD group	p value
Median age (years)	55.2	53.6	59.4	0.104
Sex				0.121
Male	64	39	25	
Female	36	28	8	
Tinnitus before SRS	77	51	26	1.000
Vertigo/disequilibrium before SRS	41	22	19	0.030
Koos grade				0.036
1	28	22	6	
2	30	16	14	
3	23	19	4	
4	19	10	9	
Median PTA at diagnosis (dB)	16.9	15.0	23.8	<0.001
Median SDS at diagnosis (%)	96.0	96.0	96.0	0.615
Median target volume (cm^3)	0.60	0.58	0.78	0.312
Median margin dose (Gy)	12.5	12.5	12.5	0.287
Median maximum dose (Gy)	25.0	25.0	25.0	0.145
Median interval between diagnosis and SRS (months)	17.4	16.8	19.1	0.245
Median follow-up after SRS (years)	4.4	4.1	5.1	0.165

Table 2. Comparison of Gardner-Robertson grade at diagnosis, SRS, and last follow-up

	Diagnosis	SRS		Last follow up	
Group	GR grade	GR grade	No. of patients	GR grade	No. of patients
HM Patients	I	I	67	I	18
				II	24
				III	22
				IV	0
				V	3
HD Patients	I	II	33	I	0
				II	8
				III	17
				IV	1
				V	7

Table 3. Univariate and multivariate analysis for serviceable hearing status after radiosurgery

Variable	Univariate	Multivariate		
	p value	p value	HR	95% CI
Age (<55 vs. ≥ 55)	0.006	0.012	2.21	1.19-4.11
Age (continuous)	0.119	NA	NA	NA
Sex	0.304	NA	NA	NA
Tinnitus before SRS (no vs. yes)	0.643	NA	NA	NA
Vertigo/disequilibrium before SRS (no vs. yes)	0.118	0.524	NA	NA
Koos grade (grade I & II vs. III & IV)	0.882	NA	NA	NA
PTA at diagnosis (<20 dB vs. ≥20 dB)	0.024	0.252	NA	NA
PTA at diagnosis (continuous)	0.025	NA	NA	NA
SDS at diagnosis (<94% vs. ≥94%)	0.603	NA	NA	NA
SDS at diagnosis (continuous)	0.835	NA	NA	NA
Target tumor volume (<0.6 cm^3 vs. ≥ 0.6 cm^3)	0.510	NA	NA	NA
Target tumor volume (continuous)	0.708	NA	NA	NA
HM group vs. HD group	<0.001	<0.001	2.85	1.68-5.41
Margin dose (<13 Gy vs. ≥13 Gy)	0.729	NA	NA	NA
Interval between diagnosis and SRS (<2 years vs. ≥2 years)	0.706	NA	NA	NA

Figures

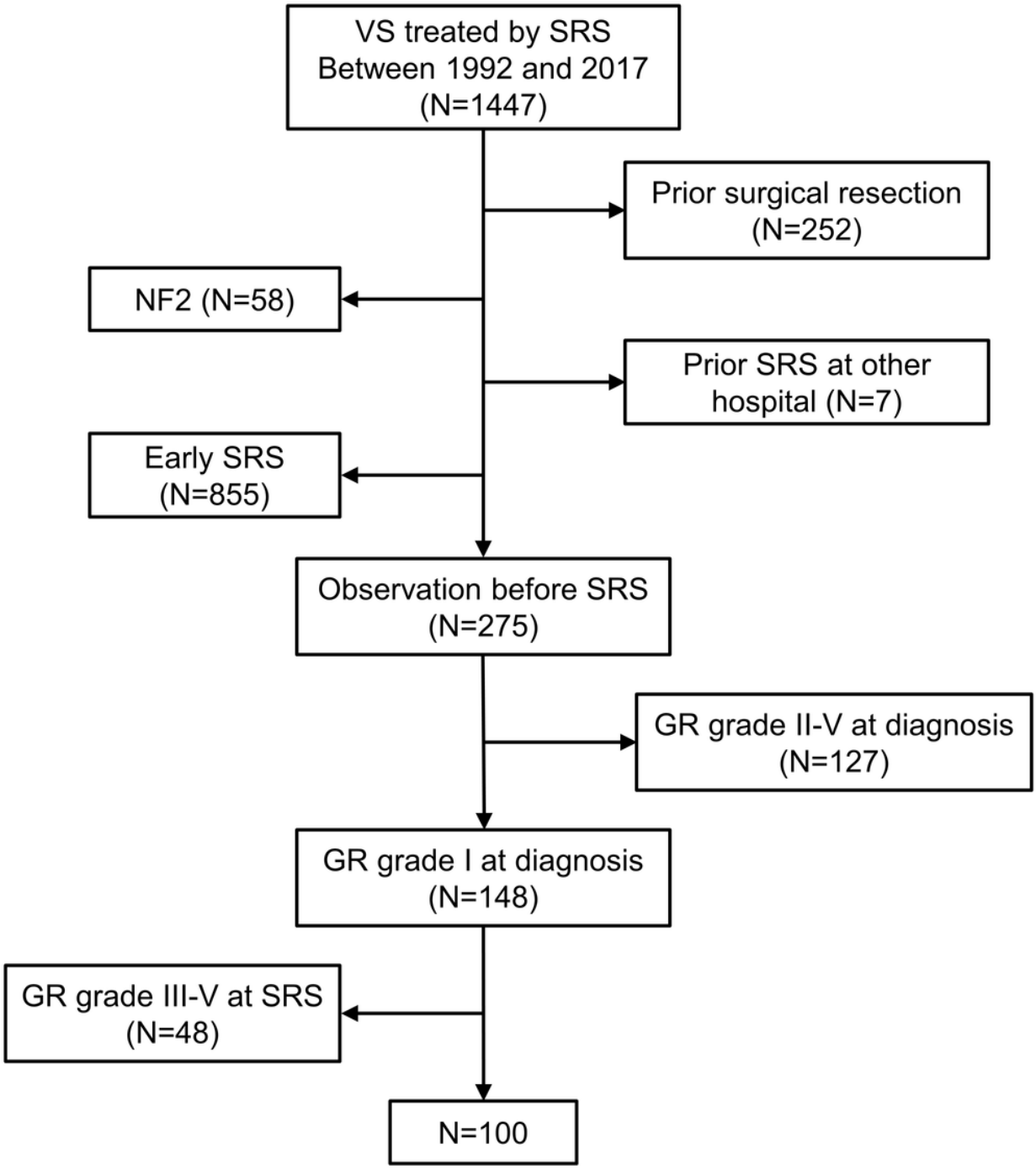

Figure 1

Flow diagram of this study population

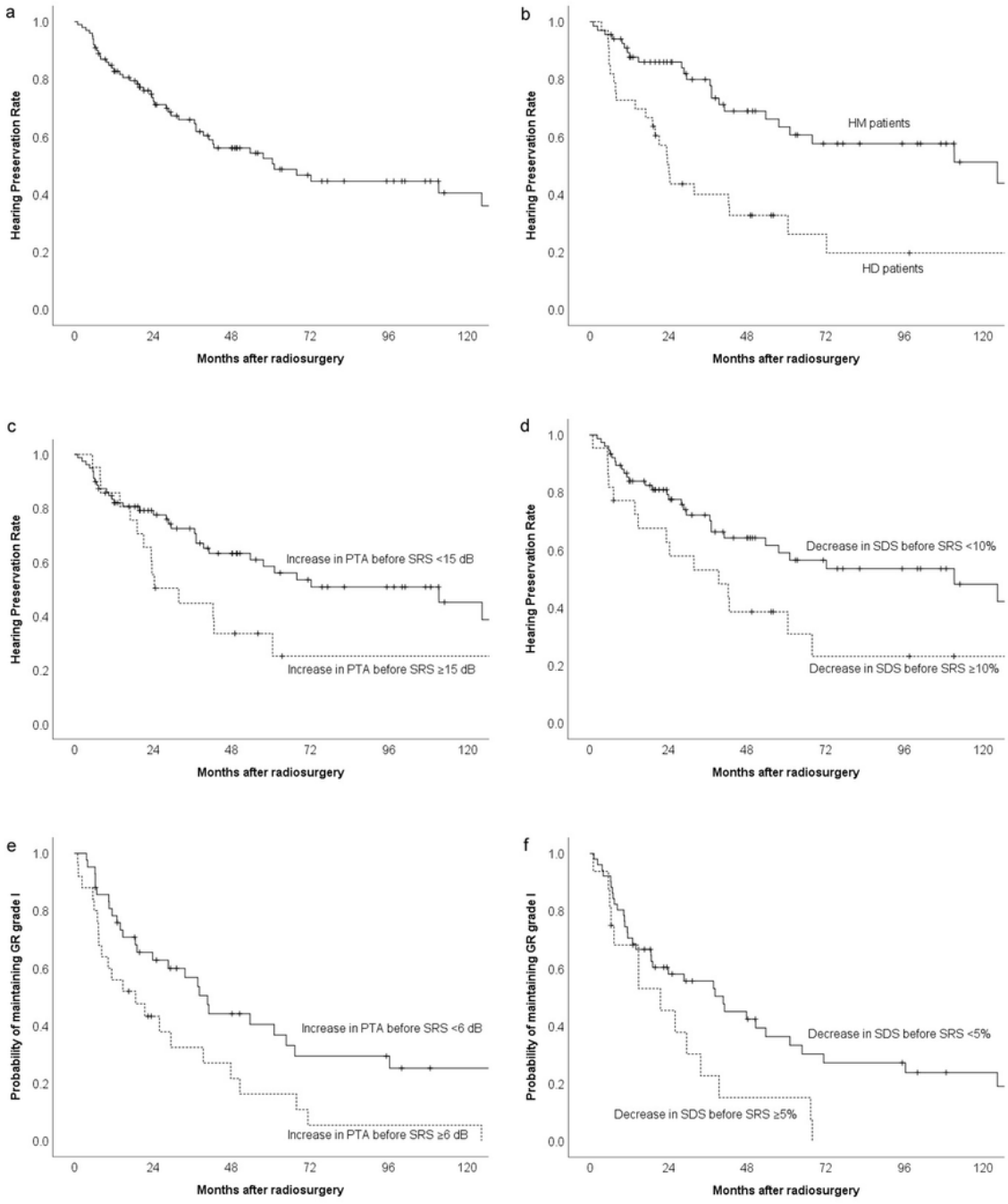

Figure 2

a: Kaplan-Meier plot demonstrating serviceable hearing preservation rate. b: Kaplan-Meier plot comparing serviceable hearing preservation rate of HM group and HD group. HM group has significantly better useful hearing preservation. c: Kaplan-Meier plot comparing serviceable hearing preservation rate of patients with increased PTA of 15 dB or more than 15 dB and less than 15 dB. Increased PTA less than 15 dB was significantly associated with a higher serviceable hearing preservation rate (p=0.011) d: Kaplan-

Meier plot comparing serviceable hearing preservation rate of patients with decreased SDS of 10% or greater than 10% and less than 10%. Decreased SDS less than 10% was significantly associated with a higher serviceable hearing preservation rate (p=0.024) e: Kaplan-Meier plot comparing probability of maintaining GR grade I of patients with increased PTA of 6 dB or greater than 6 dB and less than 6 dB. Increased PTA less than 6 dB was significantly associated with a higher probability of maintaining GR grade I (p=0.005) f: Kaplan-Meier plot comparing probability of maintaining GR grade I of patients with decreased SDS of 5% or greater than 5% and less than 5%. Decreased SDS less than 5% was significantly associated with a higher probability of maintaining GR grade I (p=0.028).