Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2011 November 15; 81(4): e497–e502. doi:10.1016/j.ijrobp.2011.05.006.

RADIOSURGERY OF GLOMUS JUGULARE TUMORS: A META-ANALYSIS

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Abstract

Purpose—During the past two decades, radiosurgery has arisen as a promising approach to the management of glomus jugulare. In the present study, we report on a systematic review and meta-analysis of the available published data on the radiosurgical management of glomus jugulare tumors.

Methods and Materials—To identify eligible studies, systematic searches of all glomus jugulare tumors treated with radiosurgery were conducted in major scientific publication databases. The data search yielded 19 studies, which were included in the meta-analysis. The data from 335 glomus jugulare patients were extracted. The fixed effects pooled proportions were calculated from the data when Cochrane's statistic was statistically insignificant and the inconsistency among studies was <25%. Bias was assessed using the Egger funnel plot test.

Results—Across all studies, 97% of patients achieved tumor control, and 95% of patients achieved clinical control. Eight studies reported a mean or median follow-up time of >36 months. In these studies, 95% of patients achieved clinical control and 96% achieved tumor control. The gamma knife, linear accelerator, and CyberKnife technologies all exhibited high rates of tumor and clinical control.

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Conflict of interest: none.

Conclusions—The present study reports the results of a meta-analysis for the radiosurgical management of glomus jugulare. Because of its high effectiveness, we suggest considering radiosurgery for the primary management of glomus jugulare tumors.

Keywords

Glomus jugulare; Radiosurgery; Gamma knife; Paraganglioma; Meta-analysis

INTRODUCTION

Glomus jugulare tumors are infrequent, indolent, and highly vascularized tumors that arise within the paraganglionic tissue of the ninth or tenth cranial nerves. When populated by chromaffin cells, they can secrete catecholamines, leading to labile blood pressure and tachycardia (1). Because of their benign histologic features, the symptoms associated with the condition are predominantly a consequence of the tumor's mass effect on local structures such as the lower cranial nerves.

Surgery was the first technique developed for the management of glomus jugulare tumors. Seiffert pioneered the surgical approach in 1934 (2), and decades of refinement have yielded incremental improvements through the advent of microsurgery and other advances, including improved neuroanesthesia, intraoperative neuromonitoring, and postoperative care. Microsurgical resection of these tumors, however, often carries considerable risk of morbidity and mortality to the patient, including cerebrospinal fluid leak, wound infection, pulmonary embolism, and lower cranial nerve deficits (3). Adjuvant treatments, such as conventional external beam radiotherapy and endovascular embolization, are also used, but these techniques also result in their own complications.

Conventional external beam radiotherapy was first applied toward the management of glomus jugulare tumors in the 1950s. Although this approach achieved satisfactory tumor control, large treatment planning margins were required, resulting in high radiation doses to the adjacent structures (1, 4, 5). A review by Springate and Weichselbaum (6) in 1990 demonstrated that conventional external beam radiotherapy resulted in at least equivalent tumor control and a lower risk of serious complication. They consequently recommended radiotherapy for the primary management of glomus jugulare. Surgery, however, has persisted as a major modality in the primary treatment of these tumors.

During the past 2 decades, radiosurgery has arisen as a promising approach to the management of glomus jugulare tumors (7). Radiosurgery provides a high degree of accuracy, exquisite precision, and rapid radiation dose falloff at the periphery of the target lesions, allowing the clinician to deliver a high radiation dose to neoplastic tissue and spare healthy brain tissue. This is particularly important in benign and indolent tumors such as glomus jugulare. Although microsurgical resection requires a prolonged inpatient hospital stay and carries the risk of perioperative complications, radiosurgery is a relatively noninvasive treatment that can be performed as an outpatient procedure. Other candidate radiation modalities include intensity-modulated radiotherapy and particle therapy. These modalities share several characteristics with radiosurgery that make them appealing alternatives, including the capacity to deliver conformal radiation doses and steep dose gradients. However, these treatments were outside the scope of the present study.

Despite the theoretical benefits of radiosurgery, a limited number of studies have reported on the use of this treatment modality to address glomus jugulare tumors. Those that have been published have been compromised by their small sample size, limited follow-up, and lack of control groups. No randomized controlled trials (RCTs) comparing the use of radiosurgery and other treatment modalities for the management of glomus jugulare tumors have been published, and all the published studies have been retrospective reviews. Most of these studies were conducted at a single institution. Furthermore, because surgery is considered the reference standard initial treatment of glomus jugulare tumors, most patients treated with radiosurgery in these studies were either poor surgical candidates or patients with recurrent or residual disease after microsurgical resection, thereby obscuring the comparison between surgery and radiosurgery. Given the paucity of data, we present a systematic review and meta-analysis of the available data on the radiosurgical management of glomus jugulare.

METHODS AND MATERIALS

To identify eligible studies, systematic searches of all glomus jugulare tumors treated with radiosurgery were conducted in the PubMed, SCOPUS, and EMBASE databases using the keywords “glomus jugulare,” “radiosurgery,” “gamma knife,” “LINAC” (linear accelerator), and “CyberKnife.” No limits were set on the date of publication or the duration of follow-up.

The studies were determined eligible for inclusion if they were original research studies that reported the results of radiosurgery for glomus jugulare tumors. Reviews were excluded. If an institution or consortium had published multiple studies, only the report with the largest sample size was included for analysis. Using this method, 47 studies were initially identified (Fig. 1) (3, 4, 7–51). From this pool, 20 reviews or off-topic studies were excluded. Of the remaining 27 studies, 8 were excluded because their results had been reported in other reports.

The data search yielded 19 studies that were included in the meta-analysis (Table 1). Of these, 14 studies used gamma knife (GK) therapy and 5 used linear accelerator-based radiosurgery (LINAC) or Cyberknife (CK). Data on 335 glomus jugulare patients were extracted, including 278 who had received GK and 57 who had received LINAC or CK. Of the 19 studies, 10 had a mean or median follow-up time >36 months.

The included studies varied considerably in both their appraisal of the data and what data was presented in the results. To standardize the results, the patients were considered to exhibit tumor control if the follow-up radiographic analysis revealed that the glomus jugulare tumor volume was equal to or less than the glomus jugulare tumor volume at radiosurgery. Similarly, a patient was considered to have achieved clinical control if the study investigator determined the patient’s clinical condition to be improved or unchanged at a follow-up examination compared with the patient’s condition at radiosurgery. A wide variance in the manner and detail of reporting acute complications and long-term sequelae across the 19 studies prevented statistical analysis of these features, but the available information from these studies is provided (Table 2).

The meta-analysis was performed by transforming proportions into the Freeman-Tukey variant of the arcsine square root-transformed proportions (52). The pooled proportion was calculated by back transforming the weighted mean of the transformed proportions. The degree of combinability of the studies was assessed by estimating the Cochrane's statistic and inconsistency (I^2) statistic. Fixed effects pooled proportions were calculated from the data when Cochrane's statistic was statistically insignifi-cant and the inconsistency among the studies (I^2) was <25%. Bias was assessed using the Egger funnel plot test (53). The statistical analysis was performed using StatsDirect Statistical Software (Cheshire, UK) (54).

RESULTS

Tumor control was defined as an unchanged or a reduced tumor volume after radiosurgery of the glomus jugulare tumor, as assessed by imaging studies. Across all studies, 97% (95% confidence interval [CI], 95–99%) of patients achieved tumor control using this definition, as estimated by the fixed effects pooled proportion (Fig. 2). The Cochran test for noncombinability was statistically insignificant (Q = 15.80, degrees of freedom, 18; p = .61). The inconsistency among the studies was estimated to be low (I^2 = 0%, 95% CI, 0–43.7%). The Egger test for bias revealed no statistically significant evidence of bias at −0.43 (95% CI, −0.97 to 0.10; p = .11).

Clinical control was defined as unchanged or improved clinical status after radiosurgical treatment of the glomus jugulare tumor. Of the patients, 95% (95% CI, 92–97%) were stable or had improved clinically (Fig. 3). This was estimated using a fixed effect model, because the Cochran test for noncombinability was statistically insignificant (Q = 10.6, degrees of freedom, 17; p = .88) and the inconsistency (I^2) was 0% (95% CI, 0–43.7%). The Egger test for bias was also statistically insignificant at −0.39 (95% CI, −1.18 to 0.36; p = .28).

Eight studies reported a mean or median follow-up time of >36 months (Table 1). For these studies, 95% of patients (95% CI, 90–98%) achieved clinical control and 96% (95% CI, 92–98%) achieved tumor control. In contrast, 11 studies reported a mean or median follow-up time of <36 months (12, 13, 16, 17, 24, 25, 27, 28, 29, 33, 34, 38, 39, 42, 43). For this group, 98% of patients achieved tumor control (95% CI, 95–100%) and 95% (95% CI, 91–98%) achieved clinical control.

Both GK and LINAC/CK technologies exhibited high rates of tumor and clinical control. Overall, patients treated with GK achieved 97% (95% CI, 94–99%) tumor control and 94% (95% CI, 91–97%) achieved clinical control. Of the patients treated with LINAC or CK, 97% (95% CI, 92–100%) achieved tumor control and 97% (95% CI, 92–100%) achieved clinical control.

DISCUSSION

The results from the present meta-analysis suggest that radiosurgery is a highly efficacious modality in the management of glomus jugulare tumors. The high success rates in tumor and clinical control in both the GK and the LINAC/CK studies for >300 patients suggest that either modality is suitable for the management of glomus jugulare tumors. With these encouraging results, the use of radiosurgery for primary management of glomus jugulare can be considered.

When possible, meta-analyses focus on RCTs and exclude other forms of studies to reduce the bias. Although this approach would be ideal, no RCTs of this condition have been published to date, owing to the rarity of glomus jugulare. Coordinating the multidisciplinary team of neurosurgery, radiation oncology, and otolaryngology further complicates this issue.

At present, radiosurgery is usually reserved for patients with contraindications for conventional surgery or with recurrent or residual disease after surgical resection. An inherent bias might be present in these data because glomus jugulare tumors refractory to surgical treatment might be more aggressive than those that are responsive to surgery. Thus, the tumor control and clinical control rates after initial treatment with radiosurgery in the entire glomus jugulare patient population might actually be better than what we have presented.

Although a formal comparison between radiosurgery and conventional surgery for the management of glomus jugulare was outside the scope of our meta-analysis, a recent surgical series has suggested that radiosurgery might offer comparable tumor control. Recently, Borba *et al.* (55) reported the results of 34 patients with glomus jugulare who underwent surgery between December 1997 and December 2007, with a mean follow-up time of 52.2 months. Of their 34 patients, 91% underwent radical resection and 9% underwent partial resection. Also, 17.6% of the patients developed a new lower cranial nerve deficit after surgery and 17.6% also developed cerebrospinal fluid leak. The tumor control rate was 94.2%.

To date, studies of the radiosurgical management of glomus jugulare tumors have been flawed by their limited sample size and focus on either the GK or LINAC/CK treatment modality. The results of our meta-analysis suggest that stereotactic radiosurgery is an effective treatment of glomus jugulare tumors. A prospective study with larger patient numbers treated with radiosurgery as a primary treatment modality and longer follow-up is the next step. Such a study would also allow for a detailed analysis of the toxicities and superior determination of clinical status by eliminating the variability in assessment and data collection exhibited by the published data currently available. Nevertheless, our results suggest that radiosurgery is effective and should be considered for primary treatment of glomus jugulare tumors.

CONCLUSIONS

The present study reports the results of a meta-analysis of the radiosurgical management of glomus jugulare. Although no RCTs have evaluated the effectiveness of this approach, the results of 335 patients in 19 studies aggregated in the present meta-analysis have demonstrated a high rate of tumor control. However, a longer period of follow-up is needed to detect the onset of secondary malignancies. At present, given the evidence of its high effectiveness, we suggest considering radiosurgery for the primary management of glomus jugulare tumors.

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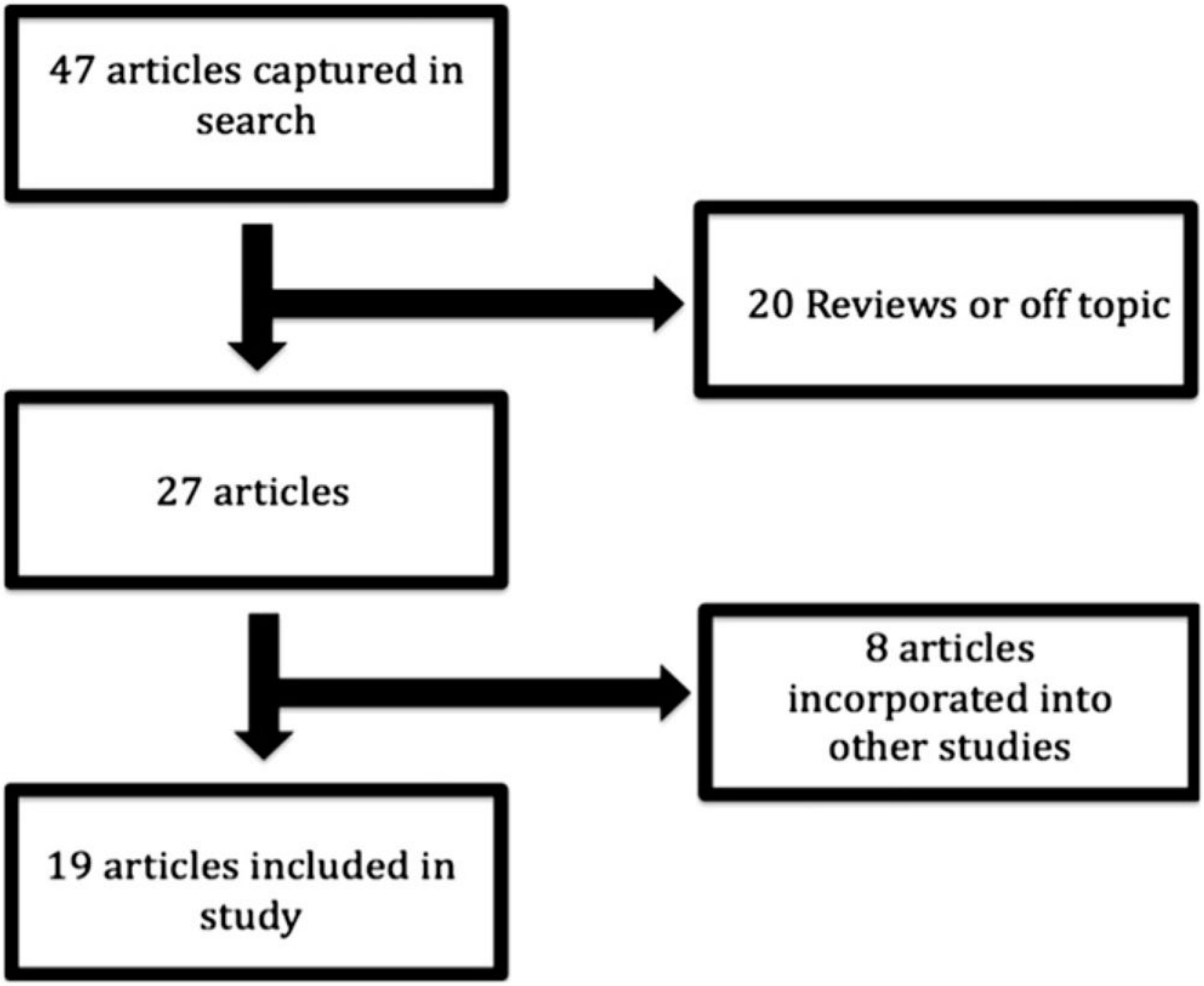

Fig. 1.
Schematic of data search.

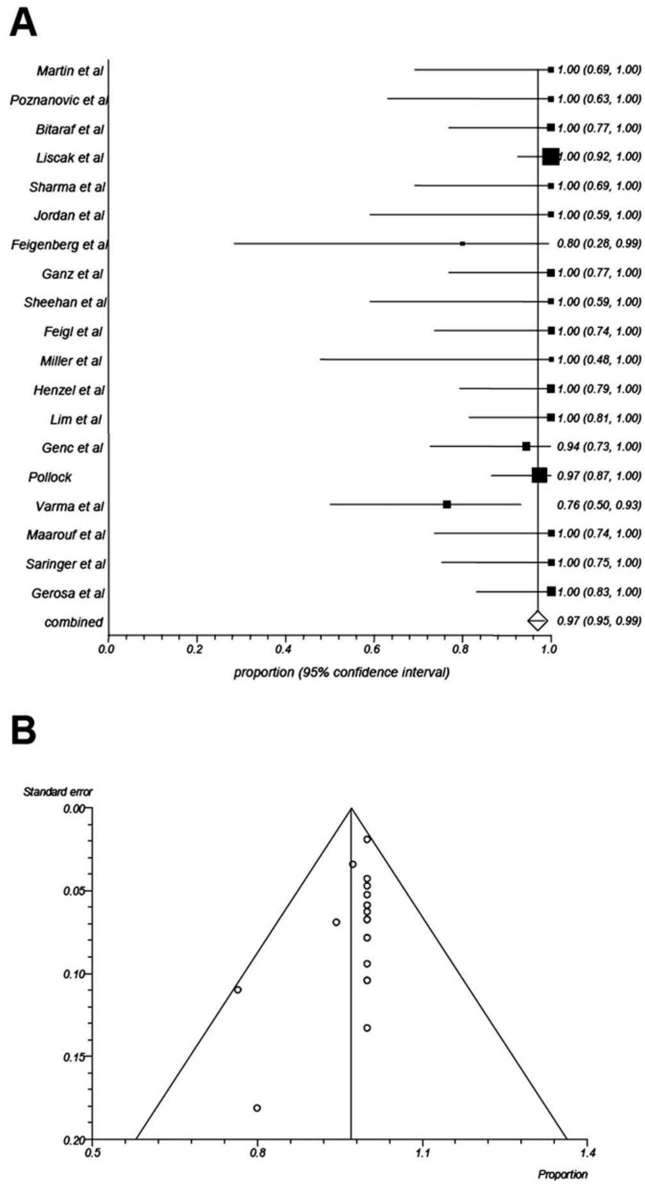

Fig. 2.

(A) Tumor control defined as unchanged or reduced tumor volume after radiosurgery of glomus jugulare tumor, as assessed by imaging studies. (B) Bias plot showing distribution of tumor control rates across studies.

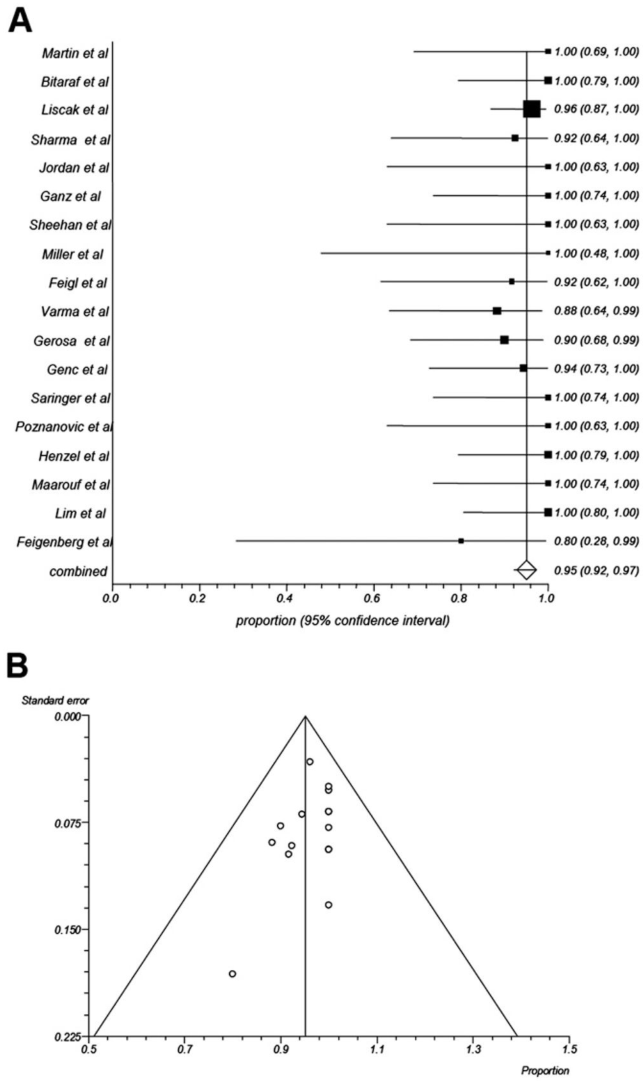

Fig. 3.

(A) Clinical control defined as unchanged or improved clinical status after radiosurgery of glomus jugulare tumor. (B) Bias plot showing distribution of tumor control rates across studies.

Table 1

Data from 19 included studies

Study	Year	Average marginal dose (Gy)	Modality	Patients (*n*)	Follow-up (mo)	Tumor control (%)	Symptom control (%)
Navarro Martin *et al.* (9)	2010	14	GK	10	10	100	100
Genc *et al.* (29)	2010	15.6	GK	18	53	94	94
Miller *et al.* (12)	2009	15	GK*	5	34	100	100
Ganz *et al.* (30)	2009	13.6	GK	14	28	100	100
Sharma *et al.* (19)	2008	16.4	GK	24	26	100	100
Lim *et al.* (34)	2007	20.4	LINAC†	18	60	100	100
Henzel *et al.* (8)	2007	Fractionated	LINAC	17	40	100	100
Gerosa *et al.* (17)	2006	17.5	GK	20	50	100	90
Varma *et al.* (13)	2006	15	GK	17	48	76	88
Poznanovic *et al.* (39)	2006	15.1	LINAC	8	16	100	100
Bitaraf *et al.* (36)	2006	18	GK	16	19	100	100
Feigl *et al.* (37)	2006	17	GK	12	33	100	92
Sheehan *et al.* (40)	2005	15	GK	8	28	100	100
Pollock (43)	2004	14.9	GK	42	44	97	NA
Maarouf *et al.* (18)	2003	15	LINAC	14	48	100	92
Feigenberg *et al.* (28)	2002	15	GK	5	27	80	80
Saringer *et al.* (25)	2001	12	GK	13	50	100	100
Jordan *et al.* (4)	2000	16.3	GK	8	27	100	100
Liscak *et al.* (14)	1999	16.5	GK	66	24	100	96

Abbreviations: GK = gamma knife; LINAC = linear accelerator; NA = not available.

* Study used combined microsurgical and radiosurgical approach.

† Conventional LINAC and CyberKnife systems included in study.

Table 2

Document complications and toxicities

Study	Year	Documented complications/toxicities affected*
Navarro Martin *et al.* (9)	2010	None
Genc *et al.* (29)	2010	None
Miller *et al.* (12)	2009	None
Ganz *et al.* (30)	2009	Transient facial palsy (1)
Sharma *et al.* (19)	2008	Trigeminal neuralgia (1)
Lim *et al.* (34)	2007	Transient tongue weakness and hearing loss (2), transient vocal cord paresis (1)
Henzel *et al.* (8)	2007	Transient low-grade nausea (6), vertigo (2), headache (2), mucositis (4)
Gerosa *et al.* (17)	2006	None
Varma *et al.* (13)	2006	None
Poznanovic *et al.* (39)	2006	Vertigo (1), transient neuropathy of cranial nerves IX, X, XII (1)
Bitaraf *et al.* (36)	2006	Vertigo (1)
Feigl *et al.* (37)	2006	Transient facial spasm (1), transient hoarseness (1)
Sheehan *et al.* (40)	2005	None
Pollock (43)	2004	Hearing loss (1), vocal cord paralysis (1), transient headache (1), nausea and vomiting (1), imbalance and vertigo (1), decreased facial sensation (1), partial hearing loss (5)
Maarouf *et al.* (18)	2003	Facial palsy (1)
Feigenberg *et al.* (28)	2002	Transient facial palsy (1)
Saringer *et al.* (25)	2001	Transient dysphagia (1), transient incomplete facial palsy (1)
Jordan *et al.* (4)	2000	Transient balance disturbance with vertigo (1)
Liscak *et al.* (14)	1999	Tinnitus (1), hearing loss (2), facial palsy (2), vertigo (2), inner ear inflammation (2)

*Data in parentheses are number of patients.