Toxicity of Gamma Knife Radiosurgery May Be Greater in Patients with Lower Cranial Nerve Schwannomas

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Abstract

Objective Gamma Knife stereotactic radiosurgery (GK-SRS) is a preferred treatment option for tumors of the jugular foramen. We hypothesized that GK-SRS toxicity is higher for lower cranial nerve schwannomas than for glomus jugulare tumors despite anatomically similar locations.

Methods We performed a retrospective review of all patients who received GK-SRS for glomus jugulare tumors and lower cranial nerve schwannomas at our institution between 2006 and 2014. Because of small sample sizes, Fisher's exact tests and logistic regression techniques were employed using SPSS.

Result We identified 20 glomus jugulare tumors and 6 lower cranial nerve schwannoma patients with a median follow-up of 17 months. Median marginal dose was 16 Gy (range 13–18 Gy) and 12.5 Gy (range 12–14 Gy), respectively. All except one patient had tumor control at last follow-up visit. No worsening of pre-existing neurological deficits was observed. There were seven patients who developed any new neurological deficit after GK-SRS, four from the glomus group, and three from the schwannoma group (20 and 50% of each group, respectively). Only two of seven patients had permanent new neurological deficits. Both of them were in the schwannoma group. Univariate analysis showed that only a diagnosis of schwannoma had a greater risk of permanent new cranial nerve complication after GK-SRS compared with diagnosis of glomus jugulare ($p = 0.046$).

Conclusion Although the marginal dose for glomus jugulare is greater, our study suggests that the risk of a new permanent neurological deficit after GK-SRS was higher in the schwannoma group compared with the glomus group.

Keywords

- ▶ glomus jugulare
- ▶ lower cranial nerve schwannoma
- ▶ stereotactic
- ▶ radiosurgery
- ▶ Gamma Knife

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Introduction

Jugular foramen tumors are uncommon, and can have varied pathology, but glomus jugulare tumors as well as lower cranial nerve schwannomas are the most common.¹ Management of these tumors is challenging because of the anatomical location that can be difficult to access surgically and the proximity of the lower cranial nerves that, if damaged, can lead to very significant morbidity. Stereotactic radiosurgery (SRS) is a treatment option with high tumor control rate and low rate of toxicity.^{2–7} Follow-up is required for adequate classification of toxicity. Although location is similar, a trend of differing toxicities is noted between glomus jugulare tumors and lower cranial nerve schwannomas. We, therefore, set out to compare the outcomes between these two groups of patients. Our hypothesis is that cranial nerve complications are higher in lower cranial nerve schwannomas compared with glomus jugulare tumors.

Materials and Methods

Patient Data Collection

The University of Pennsylvania Institute Review Board approved this retrospective review. All cases of SRS performed at Penn Gamma Knife Center at Pennsylvania Hospital were reviewed between 2006 and 2014 to identify patients who were treated for glomus jugulare or lower cranial nerve schwannoma with Gamma Knife SRS (GK-SRS).

Gamma Knife Radiosurgical Treatment

Radiosurgery was performed using a Model 4-C GK (Elekta, Inc., Stockholm, Sweden) until June 2012 when it was replaced by the Perfexion model. A Leksell stereotactic head frame (Elekta, Inc.) was applied using local anesthesia with conscious sedation. High-resolution three-dimensional magnetic resonance imaging (MRI) with gadolinium contrast were acquired at 1 or 1.5 mm interval to localize the tumor. The marginal dose was prescribed to 50% isodose line. Treatment volume was defined as the volume of tissue receiving the prescribed marginal dose or more. The treatment planning system was the Gamma Plan software (Elekta AB).

Follow-Up

Patients were typically seen at first follow-up visit in 1 to 3 months post-SRS. The first follow-up MRI was obtained in 6 to 12 months post-SRS. Toxicity was assessed using CTCAE version 4.03. Patients were routinely followed every 6 months to 1 year with MRI and clinical exam.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, United States). Fisher's exact tests were used to compare categorical variables. Logistics regression techniques were used to compare continuous variables. $p < 0.05$ was considered significant. Univariate analysis was performed to assess possible risk factors for new cranial nerve complication after GK-SRS. These factors included diagnosis, age, comorbidity, prior surgery, initial tumor volume, max-

imum tumor diameter, side of the tumor, intracranial extension, distance from brain stem, extension into cervical spine level, distance below foramen magnum, marginal tumor dose, maximum tumor dose, treatment volume, maximum brain stem dose, tumor shrinkage, and central loss of enhancement.

Results

Twenty patients with glomus jugulare and six patients with lower cranial nerve schwannoma were treated with GK-SRS between 2006 and 2014 with median follow-up time of 17 months. Nine patients in the glomus group (45%) and three patients in the schwannoma group (50%) were treated with Model 4-C GK. The rest of the patients were treated with the Perfexion model. Patient and disease characteristics are shown in ►Table 1.

Clinical Presentation

There were 37 cranial neuropathies in the glomus group, while there were 10 cranial neuropathies in the schwannoma group (►Table 2). The first and second most common presentation was tinnitus and hearing loss, respectively. These two symptoms were found in both groups of patients. Every symptom was grade 1 except four patients that had grade two hearing loss.

Radiosurgical Parameter

Details of the radiosurgical parameter was shown in ►Table 3. The tumor dose in glomus group was higher than in schwannoma group; median marginal dose 16 Gy (13–18 Gy) and 12.5 Gy (12–14 Gy), respectively. Treatment volume was larger in glomus group, which correlated with the larger tumor volume. The median maximum brain stem dose was higher in schwannoma group; 12.5 Gy (5.4–16.9 Gy) versus 4.95 Gy (1.6–10.6 Gy) ($p = 0.019$), due to the intracranial extension that approached the brain stem more than in the glomus group.

Tumor Control

The median follow-up times were 12 months (range 1–110 months) and 24.5 months (range 12–88 months) for glomus jugulare and lower cranial nerve schwannoma, respectively. Thirteen glomus jugulare patients (65%) and all six lower cranial nerve schwannoma patients (100%) had MRIs after GK-SRS. Twelve from 13 of glomus jugulare patients (92%) and all of lower cranial nerve schwannoma patients (100%) had tumor control. Two patients from the schwannoma group had decreased tumor size, while there was none in glomus jugulare group. One glomus jugulare patient had progression of tumor 2 years post-GKRS because a portion of the tumor did not receive optimal radiation dose due to avoidance of a critical structure. This patient later underwent salvage resection and had tumor control in the latest MRI follow-up.

Post-SRS Effect

There were no patients with central loss of enhancement in the glomus group. There were three patients who developed central loss of enhancement in the schwannoma group. Only one of these had significant mass effect from transient expansion of the tumor and was symptomatic.

Table 1 Patient and tumor characteristics

		Glomus jugulare (n = 20)	Lower cranial nerve schwannoma (n = 6)	p Value
		Numbers of patients (%)	Numbers of patients (%)	
Age (year)	Median (range)	62 (36–88)	46.5 (36–76)	0.126
Gender	Male	2 (10)	3 (50)	0.062
	Female	18 (90)	3 (50)	
Comorbidity	Yes	12 (60)	4 (67)	0.580
	No	8 (40)	2 (33)	
Prior surgery	Yes	3 (15)	3 (50)	0.112
	No	17 (75)	3 (50)	
Karnofsky performance status	90–100	18 (90)	6 (100)	0.585
	70–80	2 (10)	0 (0)	
Tumor diameter (cm)	Median (range)	1.7 (0.7–2.7)	2 (1.7–3)	0.281
Tumor volume (cc)	Median (range)	4.68 (0.79–9.42)	3.15 (2.64–6.78)	0.300
Laterality	Right	8 (40)	3 (50)	0.509
	Left	12 (60)	3 (50)	
Intracranial extension	Yes	4 (20)	6 (100)	0.001
	No	16 (80)	0 (0)	
Distance from brain stem (cm)	Median (range)	1.35 (0.3–2)	0 (0–0.4)	0.092
Extension into cervical spine level	Yes	14 (70)	1 (17)	0.004
	No	6 (30)	5 (83)	
Distance of cervical spine extension (cm)	Median (range)	0.625 (0.125–3.375)	0.375	0.125
	> 1 cm	5 (25)	0	0.324
	< 1 cm	15 (75)	1 (100)	

Existing Neurological Deficit Outcome

In the glomus group, the existing neurological deficits after GK-SRS were stable in 28 cranial nerves (76%) and were improved in nine cranial nerves (24%). In the schwannoma group, they were stable in five cranial nerves (50%) and were improved in five cranial nerves (50%). No worsening deficit was observed.

Newly Developed Neurological Deficit Outcome

There were seven patients (27% for both groups combined) who developed new neurological deficit after GKRS; four patients from glomus group and three patients from schwannoma group (20% and 50% of each group, respectively). The detail of new neurological deficit is shown in ► **Table 4**. Swallowing

Table 2 Clinical presentations

	Glomus jugulare (n = 20)	Lower cranial nerve schwannoma (n = 6)
Tinnitus	17	4
Hearing loss	9	4
Dizziness	3	2
Facial palsy	1	0
Swallowing difficulty	1	0
Hoarseness	3	0
Sternocleidomastoid or trapezius weakness	1	0
Tongue deviation	2	0

Table 3 Radiosurgical parameter

		Glomus jugulare (n = 20)	Lower cranial nerve schwannoma (n = 6)	p Value
Marginal tumor dose (Gy)	Median (range)	16 (13–18)	12.5 (12–14)	0.018
Maximum tumor dose (Gy)	Median (range)	32 (28–36.2)	25.3 (24–28)	0.997
Number of isocenters	Median (range)	12 (5–25)	14.5 (5–17)	0.885
Treatment volume (cc)	Median (range)	6.35 (1.52–12.88)	5.13 (3.11–7.17)	0.209
Maximum brain stem dose (Gy)	Median (range)	4.95 (1.6–10.6)	12.5 (5.4–16.9)	0.019

Table 4 Newly developed neurological deficit after Gamma Knife stereotactic radiosurgery (GK-SRS)

Patient number	Diagnosis	Symptoms	Onset post-GKRS (months)	Duration of symptom (months)	Treatment
1	Glomus jugulare	Facial numbness Facial weakness	2	2	Steroid
2	Glomus jugulare	Decreased sweet taste sensation	5	3	None
3	Glomus jugulare	Neck spasm/pain Facial weakness Swallowing difficulty	14	3	Steroid weak opioid
4	Glomus jugulare	Neck spasm/pain Swallowing difficulty Tongue weakness	8	2	Steroid
5	Schwannoma	Facial spasm and numbness ^a	36	24	None
6	Schwannoma	Swallowing difficulty	0.17	0.5	Steroid
		Vocal cord paralysis ^a	0.17	3	Laryngeal injection
7	Schwannoma	Swallowing difficulty vocal cord paralysis	0.1	4	Steroid

^aSymptoms that did not self-remit or improve with medication.

difficulty was the most frequent symptom (4 of 7 patients) and was found in both groups. Pain, facial weakness, decrease sweet taste sensation, and tongue weakness were found in the glomus group only. Two patients who developed vocal cord paralysis were both in schwannoma group, while there were none in glomus group. Most symptoms were treated with only oral steroids or just observation to resolve. One schwannoma patient who developed vocal cord paralysis, which did not resolve after steroid intake, underwent laryngeal injection to improve the voice quality. Another patient in the schwannoma group had persistent symptoms of facial spasm and numbness for at least 24 months. This patient also had central loss of enhancement with transient expansion of the tumor which still persisted but slowly resolved on MRI at 72 months post-treatment.

Risk Factors for New Neurological Deficit after GK-SRS

Univariate analysis from combining both groups showed that only diagnosis of schwannoma had a greater risk of persistent new cranial nerve complication after GK-SRS compared with diagnosis of glomus jugulare ($p = 0.046$).

Discussion

There are sufficient reviews of GKRS for schwannoma. Instead, our focus was on glomus jugulare. Many studies that review the role of SRS for glomus jugulare tumors²⁻⁵ used higher median marginal dose than in our study, ranging from 16.5 Gy to 20 Gy. They found local control rates of 100% and worsening of previously existing neurological deficit rate of 0 to 6%. The largest data are from Liscák et al² with 66 patients treated with a median marginal dose of 16.5 Gy who reported worse condition of previously existed neurological deficit in 3 of 52 patients with follow-up data available. Two of these three patients had persistent deficits. Bari et al,³ using a median

marginal dose of 20 Gy in eight patients, found one progressive worsening facial palsy after GK-SRS. This patient had undergone three operations and prior conventional fraction radiotherapy. One patient showed transient facial palsy.

In other glomus jugulare studies,⁶⁻¹¹ the median/mean marginal dose was 15 Gy, which was comparable to our study. These studies had median follow-up time ranging from 35 to 48 months. They reported local control rates of 69 to 98%, worsening of previously existing neurological deficit rate of 5 to 12%, and newly developed neurological deficit rate of 11 to 15%. In these studies, there was only one patient that developed facial numbness and no one developed swallowing difficulty. There were three patients who developed vocal cord paralysis after GK-SRS. One of these had prior external beam radiotherapy (EBRT), and another had this symptom at 1 year after the second course GK-SRS. Data from these studies and also ours showed that the rate of vocal cord paralysis after single course GK-SRS without prior EBRT in glomus jugulare patients is very low. However, swallowing difficulty was found in 2 from 13 of our glomus patients (15%), which is higher than in other studies.

Recent studies¹²⁻¹⁶ had larger sample size or longer follow-up time. They report 10-year local control rate of 69 to 94%. Ibrahim et al,¹² with sample size of 75 and median follow-up time of 51.5 months, used higher median marginal dose of 18 Gy. They reported two patients (3%) with a new permanent neurological deficit after GK-SRS. One patient had vocal cord paresis, which was treated with speech therapy. The other developed a partial facial nerve palsy. The studies by Sharma et al¹³ and Wakefield et al,¹⁴ with median marginal dose of 15 Gy, had longer median follow-up time of 62 and 123 months, respectively. The former had combined worsening and new neurological deficit of 19% which is all grade 1. The latter found only one patient (6%) that had worsening deficit and that patient was also the only

one who had tumor recurrence. All other patients who had tumor control had improved or stable neurological deficit. Winford et al¹⁵ used lower median marginal dose of 13 Gy. With median follow-up time of 26 months, they report 11 patients (29%) who developed new symptoms after GK-SRS. One patient that already had vocal cord paralysis before GK-SRS and underwent medialization laryngoplasty later.

In one study by Martin et al,¹⁶ 35 jugular schwannoma patients received radiosurgery with median marginal dose of 14 Gy (range 12–18 Gy), which is higher than our study (12.5 Gy). No patient developed a new neurological deficit and only one had a worsening of an existing neurological deficit due to tumor swelling. Zhang et al¹⁷ used GK-SRS to treat 27 jugular schwannoma patients with a mean marginal dose of 14.6 Gy (range 9.8–20 Gy). There was also no new neurological deficit or worsening of previously existing neurological deficit. These results might imply that marginal dose does not correlate with the development of new neurological deficits in jugular schwannoma patients treated with GK-SRS.

In our study, the two patients who developed new persistent neurological deficit after GK-SRS were both in the schwannoma group. One of them that had persistent new facial spasm and numbness which may be associated with an increased mass effect from radiation-induced cystic change of tumor was present during the whole course of symptoms. Longer follow-up may result in resolution of this symptom. Higher maximal brain stem dose, as shown in ▶ **Table 3**, may be the cause of new persistent neurological deficit in the schwannoma group. The median follow-up time was also twice as long in the schwannoma patients (24.5 months) versus glomus patients (12 months). Since the radiosurgery complications are typically delayed, if followed longer, more patients with glomus tumors may manifest such complications as dysphagia/dysphonia or hearing loss.

We hypothesize that one rationale for the increased development of central loss of enhancement in schwannomas compared with glomus jugulare tumors may be vascularity. Glomus tumors are usually quite vascular, while schwannomas are less so. Perhaps GK-SRS compromises the perfusion of the tumor. Glomus tumors may still have a sufficient oxygen supply due to their hypervascularity but schwannomas are more vulnerable to ischemia. When oxygenated blood delivery is reduced, glomus tumors may still have a sufficient oxygen supply, whereas schwannomas undergo necrosis where the blood supply is insufficient at its center. Further work in preclinical models will need to be done to examine the etiology of the response to SRS for these tumor types.

The large limitation to our study is the small number of patients in each group—particularly the schwannoma group. A larger multi-institutional retrospective review in Japan¹⁸ evaluated 117 patients with jugular schwannoma treated with GK-SRS. They reported 5-year progression-free survival of 89% and persistent newly developed cranial nerve deficit of 3%. The deficits are hearing disturbances, swallowing disturbances, and hypoglossal nerve palsy. There were very few patients who had worsening of existing neurological

deficit. However, this does not compare with glomus jugulare and therefore further analysis is needed to evaluate our hypothesis and possibly provide the statistical power for a definitive conclusion.

Conclusion

Although schwannoma and glomus jugulare present with tumors involving the same group of lower cranial nerves, and although the marginal dose for glomus jugulare is greater than the marginal dose for schwannomas, our study suggests that the risk of a new permanent neurological deficit after GK-SRS was higher in the schwannoma group compared with the glomus group. The rate of a new permanent neurological deficit after single course of 15 Gy GK-SRS without prior EBRT in glomus jugulare patients was very low. A larger multicenter study is needed to examine this issue further.

Conflict of Interest

We have no financial interests and no conflict of interest to disclose.

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