Stereotactic radiosurgery for jugular foramen schwannomas: an international multicenter study

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OBJECTIVE For some jugular foramen schwannomas (JFSs), complete resection is possible but may be associated with significant morbidity. Stereotactic radiosurgery (SRS) is a minimally invasive alternative or adjunct to microsurgery for JFSs. The authors reviewed clinical and imaging outcomes of SRS for patients with these tumors.

METHODS Nine participating centers of the International Gamma Knife Research Foundation identified 92 patients who underwent SRS between 1990 and 2013. Forty-one patients had prior subtotal microsurgical resection. The median interval between previous surgery and SRS was 15 months (range 0.5–144 months). Eighty-four patients had preexisting cranial nerve (CN) symptoms and signs. The median tumor volume was 4.1 cm³ (range 0.8–22.6 cm³), and the median margin dose was 12.5 Gy (range 10–18 Gy). Patients with neurofibromatosis were excluded from this study.

RESULTS The median follow-up was 51 months (range 6–266 months). Tumors regressed in 47 patients, remained stable in 33, and progressed in 12. The progression-free survival (PFS) was 93% at 3 years, 87% at 5 years, and 82% at 10 years. In the entire series, only a dumbbell shape (extension extracranially via the jugular foramen) was significantly associated with worse PFS. In the group of patients without prior microsurgery (n = 51), factors associated with better PFS included tumor volume < 6 cm³ (p = 0.037) and non-dumbbell-shaped tumors (p = 0.015). Preexisting cranial neuropathies improved in 27 patients, remained stable in 51, and worsened in 14. The CN function improved after SRS in 12% of patients at 1 year, 24% at 2 years, 27% at 3 years, and 32% at 5 years. Symptomatic adverse radiation effects occurred in 7 patients at a median of 7 months after SRS (range 5–38 months). Six patients underwent repeat SRS at a median of 64 months (range 44–134 months). Four patients underwent resection at a median of 14 months after SRS (range 8–30 months).

CONCLUSIONS Stereotactic radiosurgery proved to be a safe and effective primary or adjuvant management approach for JFSs. Long-term tumor control rates and stability or improvement in CN function were confirmed.

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KEY WORDS jugular foramen schwannoma; stereotactic radiosurgery; Gamma Knife

ABBREVIATIONS CN = cranial nerve; GKS = Gamma Knife surgery; IGKRF = International Gamma Knife Research Foundation; JFS = jugular foramen schwannoma; PFS = progression-free survival; SRS = stereotactic radiosurgery.

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JUGULAR foramen schwannomas (JFSs) are rare skull base tumors that are most often detected by imaging after patients develop gradually worsening lower cranial nerve (CN) deficits. Additional growth leads to involvement with posterior fossa neurovascular structures and brainstem compression. Microsurgical resection is a common primary approach for JFSs but may be associated with significant postoperative morbidity.^{1,2,9,12–14,16} Stereotactic radiosurgery (SRS) is a minimally invasive alternative or adjunct to microsurgery for JFSs.^{4,7,10,19} The International Gamma Knife Research Foundation (IGKRF) was established to evaluate outcomes of patients with conditions that are relatively rare and to facilitate prospective clinical trials. To better understand both the benefit and risks of SRS, we reviewed the clinical and imaging outcomes of SRS for JFS.

Methods

Patient Population

Nine participating centers in the IGKRF identified 92 patients who underwent a single-stage SRS between 1990 and 2013. All participating centers had individual internal review board approval for participation in this retrospective clinical study: University of Pittsburgh Medical Center (n = 37), Taipei Veterans Hospital (n = 16), Ruber International Hospital (n = 10), Na Homolce Hospital (n = 10), University of Virginia (n = 5), University of Pennsylvania (n = 6), Cleveland Clinic (n = 3), Université de Sherbrooke (n = 4), and New York University Langone Medical Center (n = 1). A database with selected variables was created and sent to all participating centers. Each site reviewed the medical records of these patients, entered the data in the spreadsheet, and removed all patient identifiers from the data. These de-identified data were sent to the IGKRF data-coordinating center at the University of Pittsburgh Medical Center. Patients with neurofibromatosis Type 2 were excluded from this study. Patients who underwent prior fractionated radiation therapy and staged SRS were also excluded from this study.

Radiosurgery Technique

After induction of local anesthesia supplemented by intravenous conscious sedation, all patients underwent application of an imaging-compatible stereotactic head frame, and high-resolution MRI was performed. The tumor was assessed using 1- to 2-mm contrast-enhanced volume acquisition images, supplemented by 3-mm T2-weighted scans. The SRS target was defined as the contrast-enhanced tumor volume. Radiosurgery was performed with the Model U, B, C, 4-C, or Perfexion Leksell Gamma Knife (Elekta Inc.). The median tumor volume was 4.1 cm³ (range 0.8–22.6 cm³) and the median margin dose was 12.5 Gy (range 10–18 Gy). All patients were evaluated by MRI at intervals of 3–6 months after radiosurgery. All patients had a minimum of 6 months of follow-up. The follow-up MR images were compared with the intraoperative images, and tumor dimensions were measured in the axial, sagittal, and coronal planes. Progressive disease was defined as a > 25% increase in the volume of the tumor. Before SRS and at each follow-up interval, CN and other neurological func-

tion was assessed. When clinically indicated, additional studies such as facial electromyography, audiograms, and dynamic swallowing tests were performed. Improvement of CN deficits was defined as improvement in function of at least 1 preexisting CN deficit.

For statistical analysis, we constructed Kaplan-Meier plots for progression-free survival (PFS) by using the date of SRS, the date of tumor progression, and the date of last imaging follow-up. We also constructed Kaplan-Meier plots for improvement rates of preexisting CN deficits and the development of worsening CN symptoms or signs by using the date of SRS, time to improvement or worsening of CN deficit, and time of the last clinical follow-up. Univariate analysis was performed on the Kaplan-Meier curves by using the log-rank test (categorical data) and Cox proportional-hazards models (continuous data), with $p < 0.05$ set as significant. The Mann-Whitney U-test was used to evaluate the relationship between tumor shape (dumbbell vs others) and continuous variables that included tumor volume and margin dose. Standard statistical processing software (SPSS, version 22.0; IBM Corp.) was used.

Results

Forty-one patients had undergone prior microsurgical resection (Table 1); 7 patients underwent SRS for tumor progression after microsurgery, and 34 patients underwent SRS for residual tumor after microsurgery. The median interval between previous surgery and SRS was 15 months (range 0.5–144 months). In 51 patients, the JFS was defined by imaging based on location, MRI characteristics, and growth pattern. These patients underwent SRS as the primary surgical procedure. Typically JFS shows a low T1 signal, a high T2 signal, and marked to moderate contrast enhancement on MRI sequences.^{3,8} In comparison, meningiomas have a lower T2 signal and may show calcification and often a sessile appearance because of their dural tail. Glomus jugulare tumors have more intense contrast enhancement and multiple small vascular flow voids.^{3,15,18} At the time of SRS, CN IX and X deficits were seen in 48 patients each (52%), CN VIII deficits in 42 patients (46%), CN XI deficits in 29 patients (32%), CN XII deficits in 25 patients (27%), CN VII deficits in 13 patients (14%), CN V deficits in 7 patients (8%), and CN VI deficits in 2 patients (2%) (Table 2).

Local Tumor Control

At a median of 51 months (range 6–266 months) after SRS, follow-up imaging showed tumor regression in 47 patients (51%), stability in 33 (36%), and progression in 12 (13%). The PFS was 93% at 3 years, 87% at 5 years, and 82% at 10 years (Fig. 1). In univariate analysis, only a dumbbell shape (extension extracranially via the jugular foramen) was significantly associated with worse PFS ($p = 0.021$). The 5-year PFS of patients with dumbbell-shaped tumors was 76%, whereas for those with purely intracranial tumors the PFS was 92%. The tumor volume of dumbbell-shaped tumors was significantly larger than that of non-dumbbell-shaped tumors ($p < 0.001$, median tumor volume 7.7 cm³ vs 3.3 cm³). The margin dose for dumbbell-shaped tumors was significantly lower than for smaller, non-dumbbell-shaped tumors ($p = 0.021$, median margin dose 12.5 Gy vs 13 Gy).

TABLE 1. Demographics of the patient population

Characteristic	Value
Sex	
Male	44 (48%)
Female	48 (52%)
Median age in yrs	48 (14–77)
Prior microsurgery	41 (45%)
Median interval btwn last microsurgery & SRS in mos	15 (0.5–144)
SRS for tumor progression after microsurgery	7 (8%)
SRS for residual tumor after microsurgery	34 (37%)
SRS as initial procedure	51 (55%)
Tumor Type	
A—primary intracranial	43 (47%)
B—jugular foramen w/ intracranial extension	15 (16%)
C—primary extracranial w/ foraminal extension	7 (8%)
D—intra- & extracranial extension: dumbbell shape	27 (29%)
Brainstem compression	20 (22%)
Median tumor vol in cm ³	4.1 (0.8–22.6)
Median margin dose in Gy	12.5 (10–18)
Median no. of isocenters	9 (1–27)
Median follow-up after SRS in mos	51 (6–266)

Values are expressed as the number (%) or median (range).

The other variables (sex, age, prior resection, recurrent vs residual tumors, interval between prior resection and SRS, brainstem compression, tumor volume, margin dose, and number of isocenters) were not associated with PFS.

In the group of patients without prior microsurgery (n = 51), factors associated with better PFS included tumor volume < 6 cm³ (p = 0.037) and non-dumbbell-shaped tumors (p = 0.015). The 5-year PFS of patients with tumor volume of ≥ 6 cm³ was 77%, but for those with tumor volume of < 6 cm³, it was 93% (Fig. 2). In the group of patients with prior microsurgery (n = 41), there were no significant factors associated with PFS.

Response of Preexisting CN Deficits to SRS

Eighty-four patients (91%) had CN disorders at the time of SRS. Eight patients (9%) had no neurological symptoms or signs before SRS. In these patients, their JFS was found at the time of screening imaging studies performed for unrelated indications. Twenty-seven patients (32%) with pretreatment neurological deficits had improvement. Symptom improvement occurred between 1.1 and 52.1 months (median 8.8 months) after SRS. The improvement rate of CN deficits after SRS was 12% at 1 year, 24% at 2 years, 27% at 3 years, and 33% at 5 years (Fig. 3). None of the following factors (sex, age, prior resection, recurrent vs residual tumors, interval between prior resection and SRS, brainstem compression, tumor volume, margin dose, and number of isocenters) were associated with the improvement rate of CN deficits.

The most common preexisting CN disorders were related to CN IX and X dysfunction (n = 48, 52%). Eighteen of these patients (38%) improved. The percentage of patients who had improvement in the remaining cases of CN deficits included the following: CN V in 14%, CN VI in

TABLE 2. Cranial nerve response after radiosurgery

CNs w/ Deficits	No. Before SRS	No. (%) After SRS			
		Improved	No Change	Worse	New Symptom
V	7	1 (14%)	5 (71%)	1 (14%)	2 (2%)
VI	2	1 (50%)	1 (50%)	0	1 (1%)
VII	13	4 (31%)	9 (69%)	0	0
VIII	42	8 (19%)	31 (74%)	3 (7%)	1 (1%)
IX	48	18 (38%)	26 (54%)	4 (8%)	3 (3%)
X	48	18 (38%)	28 (58%)	2 (4%)	4 (4%)
XI	29	10 (34%)	16 (55%)	3 (10%)	1 (1%)
XII	25	9 (36%)	15 (60%)	1 (4%)	2 (2%)

50%, CN VII in 31%, CN VIII in 19%, CN XI in 34%, and CN XII in 36% (Table 2).

Delayed Progression of CN Symptoms or Signs After SRS

After SRS, 14 patients (15%) had delayed onset of additional CN symptoms or signs. In 7 patients this was related to tumor progression (median of 24 months after SRS, range 6–134 months). Seven patients developed new symptoms or signs not associated with definable tumor growth. These 7 patients were found to have adverse radiation effects that developed at a median of 7 months after SRS (range 5–38 months). In all 7 patients with symptomatic adverse radiation effects, these were managed with temporary oral corticosteroids. The rate of development of new CN disorders was 8% at 1 year, 11% at 3 years, 16% at 5 years, and 16% at 10 years after SRS (Fig. 4). Factors associated with a higher rate of delayed progression of CN disorders included dumbbell-shaped tumors (p = 0.003) and measurable tumor progression (p = 0.0001). Other factors such as brainstem compression, tumor volume, margin dose, age, prior microsurgery, and preexisting CN deficits were not associated with a delayed worsening of CN function.

Additional Management

Six of 12 patients with tumor progression had repeat SRS at a median of 64 months (range 44–134 months) after their initial SRS. Four patients underwent resection at a median of 14 months after SRS (range 8–30 months). Two patients with tumor progression did not undergo any additional treatment. Because of the development of hydrocephalus in the absence of tumor progression, 1 patient required a ventriculoperitoneal shunt 7 months after SRS. Freedom from the need for additional surgical management was 94% at 3 years, 87% at 5 years, and 85% at 10 years. Characteristics of patients in whom SRS failed are shown in Table 3.

Discussion

Clinical Presentation

Jugular foramen schwannomas account for 2.9%–4% of intracranial schwannomas.^{12,17} These tumors may arise from the glossopharyngeal, vagus, or spinal accessory nerves, although it is often impossible to identify the absolute origin of the nerves.¹² The most common clinical symptoms of JFSs include lower CN dysfunction such as hoarseness and

FIG. 1. Upper: Kaplan-Meier estimate of PFS curve after SRS in patients with JFSs. **Lower:** Kaplan-Meier curves comparing PFS after SRS for dumbbell-shaped tumor versus non-dumbbell-shaped tumors.

swallowing disturbance or hearing loss developing after additional tumor growth.^{4,12,14} In the present study, the most common preexisting clinical symptom included dysfunction of CN IX and X (52%), followed by CN VIII (46%).

Microsurgical Resection

Resection has been considered the primary treatment option for JFSs. Complete resection is often difficult because of the tumor's anatomical location and its relationship

FIG. 2. In the group of patients without prior surgery, Kaplan-Meier curves comparing PFS after SRS for tumor volume of < 6 cm³ versus ≥ 6 cm³.

to adjacent critical CN, brain, and vascular structures. The tumor types have been classified by their growth pattern:^{5,11} Type A (intracranial type), Type B (intraosseous type),

Type C (extracranial type), and Type D (intra- and extracranial type). A retrosigmoid suboccipital approach¹² is often performed for Type A JFSs, Type C tumors may require

FIG. 3. Kaplan-Meier graph showing improvement rate of CN dysfunction.

FIG. 4. Upper: Kaplan-Meier graph showing deterioration rate of CN symptoms and signs after SRS. **Lower:** Kaplan-Meier curves comparing the symptomatic deterioration rate after SRS for dumbbell-shaped tumor versus non-dumbbell-shaped tumors.

an infratemporal fossa approach,² whereas a combined retrosigmoid and infratemporal approach may be needed for tumor Types B and D.⁶ Neuromonitoring and image guidance have assisted microsurgical resection of JFSs, with

improvement in outcomes. In recent studies, transient CN VII deficits after microsurgery varied from 11% to 80% and permanent CN VII deficits ranged from 4% to 20%.^{1,2,9,13,14,16} Transient CN VIII deficits after microsurgery varied from

TABLE 3. Characteristics of patients with failed SRS

Case No.	Age/ Sex	Prior Surgical Removal	Preexisting CN Deficits	Dumbbell Shape	Tumor Vol (cm ³)	Margin Dose (Gy)	PD After SRS (mos)	CN Deficits at Last FU	Duration of Symptom Deterioration (mos)	Post-GKS Modality	Time Btwn SRS & Post-SRS Modality (mos)
1	56/F	No	No	Yes	13.9	12.0	6.0	CN IX, X	6.0	Repeat SRS	12.0
2	48/M	No	No	Yes	3.3	12.5	41.0	CN IX, X	41.0	No	NA
3	70/M	Partial	CN VIII–XII	Yes	17.0	12.5	42.0	CN VIII–XII	38.0	Repeat SRS	44.0
4	62/F	No	CN IX–XI	Yes	6.1	12.5	61.0	CN IX–XI	Stable	No	NA
5	47/F	Partial	CN IX–XII	No	0.93	16.0	6.1	CN IX–XII	Stable	Craniotomy	8.1
6	42/M	No	CN IX–XII	Yes	6.3	10.0	7.7	CN IX–XII	7.7	Craniotomy	16.3
7	42/M	Partial	CN IX–CN XI	No	1.9	13.0	48.1	CN IX–XI	Stable	Repeat SRS	55.1
8	47/F	No	CN VIII	Yes	2.6	13.0	134.0	CN VIII	134.0	Repeat SRS	134.0
9	53/F	No	CN V, IX–XII	No	6.1	13.0	12.0	CN V, IX–XI	12.0	No	NA
10	46/F	No	CN XII	Yes	8.5	12.5	9.6	No	Improved	No	NA
11	47/F	Partial	No	No	3.9	12.0	72.0	No	NA	Repeat SRS	72.0
12	42/F	No	CN VIII	No	6.5	12.5	30.0	CN VIII–XI	30.0	Craniotomy	30.0
13	53/F	Partial	CN IX–XI	No	1.5	13.0	NA	CN V, IX–XII	38.1	No	NA
14	72/M	No	CN VIII	Yes	4.0	13.5	NA	CN VIII, X	8.0	No	NA
15	41/M	Partial	CN V, VII–XI	Yes	16.0	12.0	NA	CN V, VII–XI	6.0	No	NA
16	67/M	No	No	Yes	9.8	12.0	NA	Unsteady gait	6.0	VP shunt	7.0
17	33/M	Partial	CN V, VII, IX, X	Yes	5.1	16.0	NA	CN V–VII, IX, X	136.2	No	NA
18	19/F	Total	CN VI–XII	No	11.1	12.0	NA	CN VI–XII	24.0	No	NA
19	60/F	No	No	No	1.4	12.5	NA	CN VIII	5.0	No	NA

FU = follow-up; NA = not applicable; PD = progressive disease.

8% to 45% and permanent CN VIII deficits after microsurgery varied from 4% to 20%. Transient lower CN (CN IX–XI) deficits varied from 25% to 60% and permanent CN IX–XI deficits varied from 10% to 48%.

Sanna et al.¹³ reported 23 patients with JFS who underwent microsurgical resection. Sixteen patients were found to have at least 1 CN deficit in the preoperative evaluation. A new deficit of the lower CNs developed in 11 patients after microsurgery. Bulsara et al.¹ reported 53 patients with JFS who underwent microsurgical resection, and 48 of these patients (91%) achieved gross-total resection. The deterioration of CN IX and X was seen in 16 patients (30%), with 26% of the deficits being permanent. Three patients (6%) experienced tumor recurrence at a mean follow-up period of 8.4 years. Three patients (6%) developed CSF leaks and required reoperation with primary closure of the dural defect. Sedney et al.¹⁴ reported 81 patients with JFS who underwent microsurgery, and mentioned that a conservative surgical approach resulted in a statistically significant decrease in lower CN deficits compared with radical gross-total resection. The strategy of radical resection has gradually been replaced by a more conservative surgical approach to preserve CN function.

Stereotactic Radiosurgery

Gamma Knife surgery (GKS) has a high tumor control rate, a high rate of CN preservation, and low morbidity.^{4,7,10,19} Recently, SRS has been used as a primary treatment for medium to small JFSs and as a secondary treatment for residual or recurrent JFSs after microsurgery. Zhang et al.¹⁹ reported 27 patients with JFS who underwent SRS (2 of

whom were not followed), with a mean follow-up of 38.7 months. Tumors regressed in 11 patients, remained stable in 13, and enlarged in 1 patient, who underwent a second SRS procedure. Sixteen patients improved and 9 remained at their pre-SRS clinical status. No patient developed new CN deficits after SRS. Martin et al.⁷ reported 34 patients with JFS with 35 tumors who underwent GKS. The 10-year PFS was 94%, with a mean follow-up of 84 months. There were 6 patients with neurofibromatosis Type 2 in their study. All of the patients without neurofibromatosis were in the present study. Peker et al.¹⁰ reported 17 patients with JFS who underwent GKS. The tumor growth control rate was 100%, with a mean follow-up of 64 months. Six patients (35%) had improvement of preexisting neurological deficits. Only 1 patient had transient hoarseness.

Recently, Hasegawa et al.⁴ reported the results of an 18-institution Japanese multicenter JFS study in which 117 patients underwent SRS, with a median follow-up of 52 months. Tumor regression was found in 53% and tumor progression was detected in 11%. The PFS was 91% at 3 years and 89% at 5 years. In our study, tumors regressed in 51% and progressed in 13% at a median follow-up of 51 months. The PFS was 93% at 3 years, 87% at 5 years, and 82% at 10 years. Tumor control data in the Japanese study were similar to those in our present study. Hasegawa et al. also reported that 20 patients (17%) developed some degree of symptomatic deterioration after SRS. In the present study, 14 patients (15%) had delayed onset of additional CN symptoms or signs. Additionally, we found that dumbbell-shaped tumors had a higher rate of progression (Fig. 1). The median volume of dumbbell-shaped tumors was sig-

nificantly larger than that of non-dumbbell-shaped tumors ($p < 0.001$, 7.7 cm^3 vs 3.3 cm^3). The median margin dose for dumbbell-shaped tumors was lower ($p = 0.021$, median margin dose 12.5 Gy vs 13 Gy). This may indicate that perhaps dumbbell-shaped tumors had a worse PFS because their larger volumes were treated with lower margin doses. We also found that dumbbell-shaped tumors were significantly associated with a higher rate of symptomatic deterioration (Fig. 4). We suspect that non-dumbbell-shaped tumors are recognized at an earlier stage, which facilitates earlier and more successful intervention with SRS.

Hasegawa et al.⁴ reported that preexisting hoarseness and swallowing disturbances improved in 66% and 63% of the patients, respectively. In the present study, 18 of 48 patients (38%) who had preexisting CN IX and X deficits improved. The rates of improvement in lower CN function in the report by Hasegawa et al. were significantly higher than those in the present study. This might have been caused by the fact that there are no well-established grading scales for lower CN dysfunction. Therefore, especially in a multi-institutional study, the subjective evaluation for lower CN dysfunction might vary by institution. We believe that the Kaplan-Meier method is a superior way to demonstrate the time course of potential CN symptom improvement after SRS. We found that the improvement rate of CN deficits after SRS was 12% at 1 year, 24% at 2 years, 27% at 3 years, and 33% at 5 years.

Study Limitations

The limitations of this study include the inherent differences in patient selection and treatment afforded by a retrospective multicenter study. In addition, the length of follow-up for some of the patients was < 12 months, thereby making it difficult to determine the effect of treatment versus the natural history of a skull base tumor such as a JFS. Some tumors were diagnosed by imaging and clinical history, posing the possibility that they in fact were not JFSs. Radiographic and clinical reviews of each case were performed by each participating center. Finally, neuroimaging and radiosurgical techniques have changed over the years. These changes have probably led to earlier detection of JFSs and facilitated improvements in radiosurgical technique.

Conclusions

Stereotactic radiosurgery provided a satisfactory benefit to the risk profile for patients with residual or newly diagnosed, small-volume, skull base JFSs in this multicenter experience. After SRS, 32% of the patients with pretreatment neurological deficits had improvement, but 15% of the patients had delayed onset of additional CN symptoms or signs. The best results were associated with patients with smaller-volume tumors that were detected earlier and had not extended extracranially.

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Disclosures

Dr. Lunsford is a stockholder with AB Elekta and a consultant for Insightec, DSMB. Dr. Liscak is a consultant for Elekta AB.

Author Contributions

Conception and design: Kano. Acquisition of data: Kano, Meola, Yang, Guo, Martínez-Alvarez, Martínez-Moreno, Urgosik, Liscak, Cohen-Inbar, Sheehan, Lee, Abbassy, Barnett, Mathieu, Kondziolka. Analysis and interpretation of data: Kano. Drafting the article: Kano, Lunsford. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors.

Approved the final version of the manuscript on behalf of all authors: Kano. Statistical analysis: Kano. Study supervision: Kano.

Supplemental Information

Previous Presentations

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