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Long-term outcomes after radiosurgery for glomus jugulare tumors

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Abstract

Aims and background: The treatment of glomus jugulare tumors (GJT) remains controversial due to high morbidity. Historically, these tumors have primarily been managed surgically. The purpose of this retrospective review was to assess the tumor and clinical control rates as well as long-term toxicity of GJT treated with radiosurgery.

Methods: Between 1993 and 2014, 30 patients with GJT (31 tumors) were managed with radiosurgery. Twenty-one patients were female and the median age was 59 years. Twenty-eight patients (93%) were treated with radiosurgery, typically at 14 Gy (n = 26), and 2 patients (7%) with stereotactic radiosurgery. Sixteen cases (52%) had undergone prior surgery.

Results: The mean follow-up was 4.6 years (range 1.5–12). Crude overall survival, tumor control, clinical control, and long-term grade 1 toxicity rates were 97%, 97%, 97%, and 13% (4/30), respectively. No statistically significant risk factor was associated with lower tumor control in our series. Univariate analysis showed a statistically significant association between patients having 1 cranial nerve (CN) involvement before radiosurgery and a higher risk of lack of improvement of symptoms (odds ratio 5.24, 95% confidence interval 1.06–25.97, p = .043).

Conclusions: Radiosurgery is an effective and safe treatment modality for GJT. Patients having 1 CN involvement before radiosurgery show a higher risk of lack of improvement of symptoms.

Keywords

Radiosurgery, glomus jugulare tumor, paraganglioma, outcome

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Introduction

Glomus jugulare tumors (GJT), also known as paragangliomas, are tumors derived from paraganglionic cells located in the jugular foramen.[1] Frequently, this disease has a benign behavior and only between 2% and 4% may have malignant behavior.[2] These tumors represent .6% of all head and neck tumors, appearing most frequently between the fifth and sixth decade of life, are more common in women than men by a ratio of 3–6 to 1, and may have a

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Table 1. Characteristics of patients treated for glomus jugulare tumors.

Characteristics	Patients (n = 30), n (%) or median (range)
Age, y	59 (18–79)
Sex	
Female	21 (70)
Male	9 (30)
Side[a]	
Left	14 (45)
Right	17 (55)
Tinnitus before SRS	
Yes	12 (40)
No	18 (60)
CN involvement before SRS[a,b]	
CN V	4 (13)
CN VI	1 (3)
CN VII	9 (29)
CN VIII	21 (68)
CN IX	10 (32)
CN X	10 (32)
CN XI	5 (16)
CN XII	6 (19)
None	2 (6)
Hearing impairment before SRS	
Hearing loss	12 (40)
Deafness	10 (33)
None	8 (27)
Prior surgery[a]	
Complete resection	4 (13)
Partial resection	12 (39)
No	15 (48)
Pre-SRS tumor volume, mL[a]	56 (.4–462.4)
Radiotherapy machine[a]	
Cyberknife	2 (10)
Linear accelerator	29 (90)
SRS dose, Gy[a]	
12	2 (6)
14	26 (84)
24	2 (6)
27	1 (3)
Maximum radiation dose, Gy	16 (14–33)
Prescription isodose, %	90 (50–90)

Abbreviations: CN: cranial nerve; SRS: stereotactic radiosurgery.
[a]A total of 31 glomus jugulare tumors were treated in 30 patients.
[b]Patients may have had more than 1 CN deficit.

genetic association.[3,4] Initially they are asymptomatic until they erode the bone in the jugular foramen. Although benign, these tumors sometimes present rapid growth with neurologic symptoms such as hearing loss, cerebral nerve palsies, and tinnitus. It is reported that up to 4% may have catecholamine secretion, causing instability in blood pressure, tremor, anxiety, flushing, and tachycardia.[4]

Treatment of GJT is complex and controversial. The modalities of treatment are observation, surgery with or without embolization, radiosurgery, and conventional radiation therapy.[1,3–10] Conservative observation of GJT was seldom used as these tumors tend to grow, thus it is better to treat them as soon as possible. Despite major technical advances in surgery and the use of perioperative arterial embolization to decrease bleeding, there is still significant morbidity. The anatomical relationships of the tumor, particularly cerebrovascular structures (i.e., jugular vein) and cranial nerves (CN), increase the risk of toxicity and make it difficult to achieve complete resection safely.[11–13]

Conventionally, fractionated radiation therapy has been previously used after surgery in case of a partial resection or a recurrence. In the last 2 decades, the advent of radiosurgery as treatment of tumor lesions with small volume has replaced conventional radiotherapy, with satisfactory results.

There are limited long-term data reporting the long-term outcomes of radiosurgery. This study presents our institution's experience in the treatment of GJT with this radiation technique.

Methods

From 1993 to 2014, 30 patients with GJT with 31 tumors were treated with radiosurgery. All cases had clinical follow-up and MRI during at least 18 months after treatment. All patients gave informed consent for the treatment. Case notes, medical images, and reports were reviewed and the relevant information extracted. Approval was granted by the Research Ethics Committee prior to data collection. Table 1 shows patient characteristics. The median volume of GJTs was 56 mL, ranging from .4 to 462.4 mL. All patients had neurologic symptoms before radiosurgery. The most common CN involvement was the VIII CN in 68% (n = 21) of patients. Forty percent (n = 12) had hearing loss and tinnitus while 33% (n = 10) had deafness. No patient presented with compression of the cerebral cortex, hydrocephalus, or catecholamine-secreting GJTs.

Treatment

Different treatment options (surgery with or without embolization, radiosurgery, and conventional radiation therapy) were offered to the patients and treatment with radiosurgery was jointly decided. A 6 MV linear accelerator with a high-precision mechanical fastening (SRS 200, University of Florida, Gainesville) was used for 29 patients (94%). We started using the CyberKnife system (Accuray, Sunnyvale, CA) in 2011. Since then, patients (n = 2) are treated with this frameless system. Pretreatment imaging included MRI and CT scan. Before treatment, T1- and T2-weighted volumetric MRI sequences are obtained while the patient is wearing a stereotactic head frame, and the tumor is then carefully analyzed by a neurosurgeon and radiation oncologist to identify a treatment plan that will effectively treat the tumor and avoid adjacent tissue. No

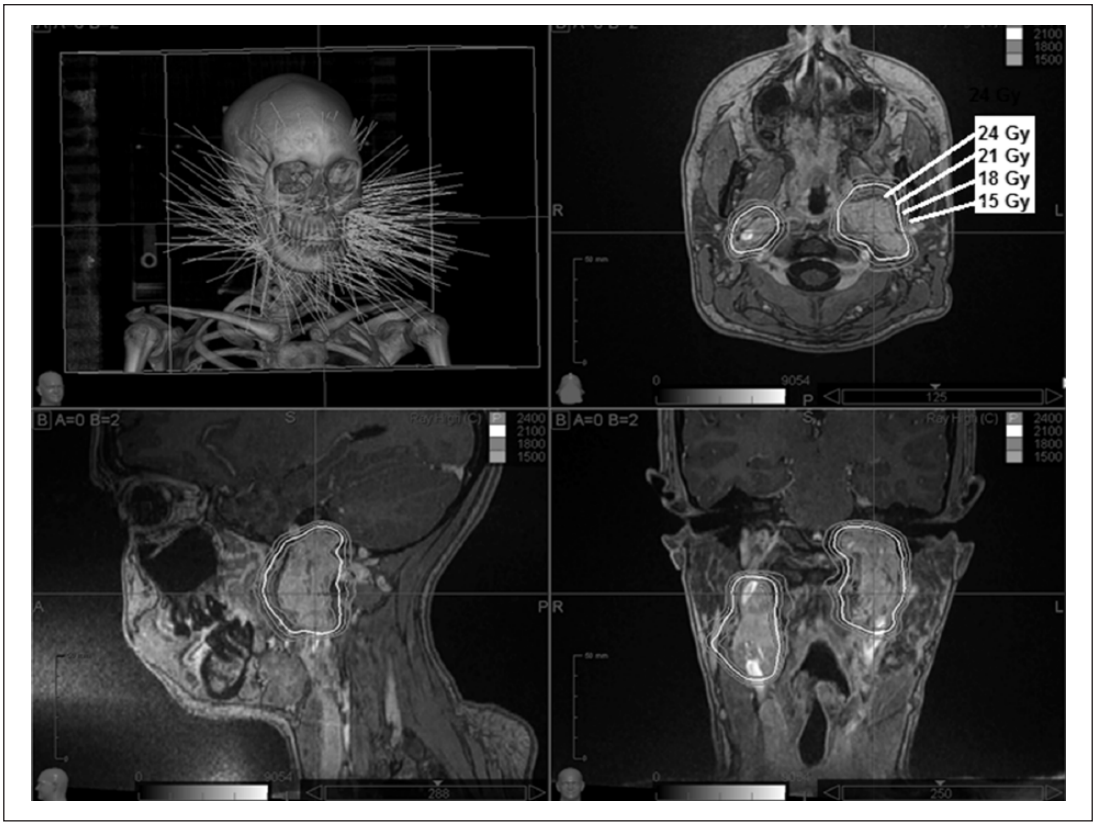

Figure 1. Planning image showing dose distribution encompassing a bilateral glomus jugulare tumor. This patient was treated with CyberKnife to 24 Gy in 3 fractions prescribed to the 82% isodose line.

margins were used for the radiosurgery planning. Three-dimensional treatment planning was done in all cases, using different planning units (Philips SRS 200 [Philips, Madison, WI], Brain Lab [Brain-Lab, Feldkirchen, Germany], Plato-Nucletron [Nucletron, Veenendaal, Netherlands], and ERGO-3D Line [3Dline Medical Systems, Milan, Italy]) during the period of the study. The prescription dose was 14 Gy in 26 radiosurgeries (84%) and 12 Gy in 2 cases (6%). In addition, 2 patients received treatment with hypofractionated CyberKnife over 3 GJTs without stereotactic frame. The patient with 2 GJTs (Figure 1) received 24 Gy delivered in 3 fractions while the remaining patient received 27 Gy in 3 fractions. The median prescription isodose was 90%, ranging between 50% and 90%, and the median maximum dose achieved was 16 Gy (range 14–33 Gy). Besides tumor volume, the maximum doses at adjacent structures, such as the optic chiasm or optic nerves, were calculated. After radiosurgery, all patients were subjected to prophylactic treatment with dexamethasone and remained in the hospital for 24 hours in case of early complications.

Follow-up

Patients were reviewed by the multidisciplinary team of radiation oncologists and referring surgeons 4 to 6 weeks following completion of treatment and annually unless otherwise clinically indicated. Tumor control was defined as an unchanged or reduced tumor size after radiation to the GJT, as assessed by imaging. Clinical control was defined as an unchanged or improved clinical status after radiation treatment. This was determined by an objective change in the patients' physical examination or a change in symptoms. Long-term toxicity was defined according to the Radiation Therapy Oncology Group criteria.

Statistical analysis

All data analyses were done using SPSS (version 19.0) statistical software. Cox proportional hazards analysis was performed to calculate odds ratios (ORs) and confidence intervals (CIs) to evaluate the influence of patient, tumor, and treatment characteristics on the control of tumor and symptoms. A p value of less than .05 was considered statistically significant.

Results

The median age of patients was 59 years, with a minimum age of 18 years and a maximum of 79 years, being typically women (n = 21; 70%). The GJT was on the right side in 55% of cases (n = 17). Sixteen patients (52%)

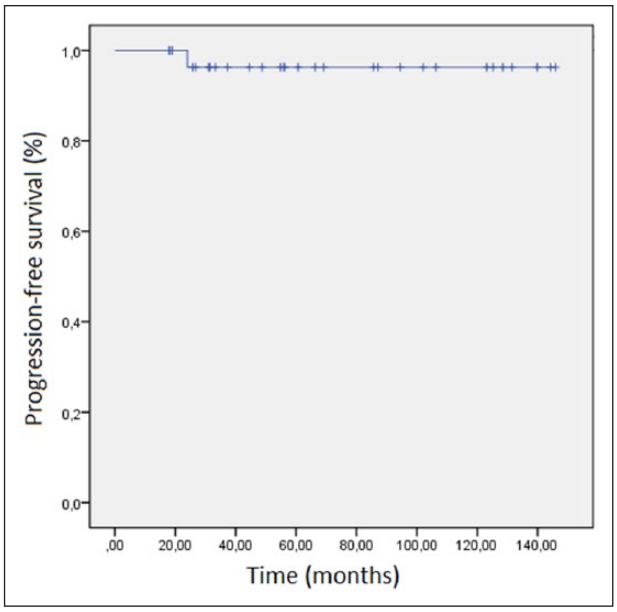

Figure 2. Kaplan-Meier curve for all 30 patients with glomus jugulare tumors for progression-free survival.

underwent prior surgery according to reports from neurosurgeons with 12 and 4 partial and complete resections, respectively. Additionally, 6 (38%) out of the 16 operated patients underwent preoperative transarterial embolization and reoperation was performed in 5 patients (31%) because of tumor recurrence. Postoperative CN deficits were reported in all patients (Table 1). Two patients (7%) had received prior conventional fractionated radiotherapy 5 (56 Gy) and 8 (50 Gy) years before radiosurgery, respectively. Moreover, a patient was treated with Gamma Knife radiosurgery 8 years before (unknown dose).

The mean follow-up was 4.6 years (range 1.5–12 years); during this period, overall symptom control was achieved in 96.8% of patients, as 48.4% (n = 15) improved, 48.4% (n = 15) were unchanged, and only 3.2% (n = 1) worsened. The overall tumor control by MRI was 96.7%, of which in 67.7% (n = 21) the lesion remained stable and 29% (n = 9) showed size reduction without in any case showing a disappearance of the tumor. Only 1 lesion recurred (3.2%; Figure 2). The progression case was a young (39 years old) man who had the larger GJT volume of this series (462 mL). After a partial resection, the patient was treated with 14 Gy at the 55% isodose line. A second radiosurgical treatment was performed 2 years later and was ineffective, resulting in death 3 years after the initial treatment. There were no statistically significant clinical or therapeutic risk factors associated with tumor control in our series (factors listed in Table 2). Univariate analysis (Table 3) showed a statistically significant association between patients having 1 CN involvement before radiosurgery (Table 4) and a higher risk of lack of improvement of symptoms (OR 5.24, 95% CI 1.06–25.97, p = .043).

Table 2. Univariate analysis of factors associated with tumor control (decrease in size vs stable/growth).

Characteristic	OR	95% CI		p Value
Sex				
Female	1.000			
Male	1.029	.160	6.620	.976
Age, y				
< Median	1.000			
≥ Median	.309	.054	1.753	.185
Prior surgery				
No	1.000			
Yes	.750	.137	4.095	.740
Tinnitus before SRS				
No	1.000			
Yes	.800	.145	4.423	.798
Hearing impairments before SRS				
No	1.000			
Yes	4.000	.689	23.229	.122
CN VII involvement before SRS				
No	1.000			
Yes	1.029	.160	6.620	.976
CN VIII involvement before SRS				
No	1.000			
Yes	.278	.029	2.696	.269
CN IX involvement before SRS				
No	1.000			
Yes	.549	.097	3.117	.499
CN X involvement before SRS				
No	1.000			
Yes	1.250	0.197	7.921	0.813
One CN involvement before SRS				
No	1.000			
Yes	1.128	0.206	6.168	0.889
Pre-SRS tumor volume, mL				
< Median	1.000			
≥ Median	0.338	0.055	2.101	0.245
Maximum radiation dose, Gy				
< Median	1.000			
≥ Median	0.667	0.106	4.182	0.665
Prescription isodose, %				
< Median	1.000			
≥ Median	0.667	0.106	4.182	0.655

Abbreviations: CI: confidence interval; CN: cranial nerve; OR: odds ratio; SRS: stereotactic radiosurgery.

Toxicity was experienced by 12.9% (n = 4) of patients and all cases were grade 1, with a median time of onset of toxicity of 4.9 months, ranging between 1.2 and 6.6 months, although improvement was achieved without complications. There was no late toxicity in any patient.

Table 3. Univariate analysis of factors associated with clinical control (improvement vs stable/worse).

Characteristic	OR	95% CI		*p* Value
Sex				
Female	1.00			
Male	.46	.09	2.21	.330
Age, y				
< Median	1.00			
≥ Median	.80	.18	3.54	.769
Prior surgery				
No	1.00			
Yes	.86	.21	3.58	.833
Tinnitus before SRS	1.00	.40	8.07	.443
No	1.80			
Yes				
Hearing impairments before SRS				
No	1.00			
Yes	1.62	.36	7.43	.531
CN VII involvement before SRS				
No	1.00			
Yes	.23	.04	1.22	.233
CN VIII involvement before SRS				
No	1.00			
Yes	.89	.19	4.11	.880
CN IX involvement before SRS				
No	1.00			
Yes	.62	.13	2.82	.531
CN X involvement before SRS				
No	1.00			
Yes	1.12	.24	5.21	.880
One CN involvement before SRS[a]				
No	1.00			
Yes	5.24	1.06	25.97	.043
Pre-SRS tumor volume, mL				
< Median	1.00			
≥ Median	.86	.21	3.58	.833
Maximum radiation dose, Gy				
< Median	1.00			
≥ Median	.38	.08	1.84	.227
Prescription isodose, %				
< Median	1.00			
≥ Median	1.25	.28	5.53	.769

Abbreviations: CI: confidence interval; CN: cranial nerve; OR: odds ratio; SRS: stereotactic radiosurgery.
[a]A patient without CN involvement before SRS was not included in the analysis.

Table 4. Pretreatment and posttreatment clinical/neurologic status.

Patient	Clinical/neurologic status			
	Pre-SRS			Post-SRS
	Tinnitus	Audition	CN involvement	
1	No	Hearing loss	V-VI-VIII-IX-X	Improved
2	Yes	Deafness	VIII	Improved
3	No	Normal	VII-IX-X-XII	Improved
4	No	Deafness	VII-VIII	Improved
5	No	Deafness	VII-VIII	Worst
6	No	Hearing loss	VII-VIII	Improved
7	No	Hearing loss	VII-VIII	Improved
8	No	Hearing loss	VIII	Stable
9	No	Deafness	VIII	Stable
10	Yes	Deafness	VIII-IX-X	Stable
11	Yes	Hearing loss	VIII	Stable
12	No	Hearing loss	VIII	Improved
13	No	Normal	IX-X-XI-XII	Stable
14	Yes	Hearing loss	VIII	Stable
15	No	Normal	IX-X-XI	Stable
16	No	Deafness	V-VII-VIII-IX-X-XI-XII	Improved
17	No	Deafness	V-VII-VIII-XII	Improved
19	No	Deafness	VII-VIII-IX-X-XI	Stable
19	No	Deafness	V-VIII-IX-XII	Improved
20	Yes	Normal	XII	Improved
21	No	Normal	X	Stable
22	Yes	Hearing loss	VII	Stable
23	No	Hearing loss	VIII	Stable
24	Yes	Hearing loss	VIII	Stable
25	Yes	Hearing loss	VIII	Stable
26	Yes	Deafness	VIII	Stable
27	Yes	Normal	NA	Improved
28	Yes	Normal	IX-X	Improved
29	No	Hearing loss	VIII	Stable
30	Yes	Normal	None	Stable

Abbreviations: CN: cranial nerve; SRS: stereotactic radiosurgery.

Discussion

The GJT is located in the jugular foramen derived from non-neuronal paraganglionic cells, which in turn are derived from neural crest cells.[1,3] GJT treatment is highly complex and controversial[14] and is supported only in retrospective studies and case series. No prospective studies are related to its treatment. Conservative management can be

taken as a therapeutic approach,[15] open surgery,[16–20] conventional radiation therapy,[21,22] and radiosurgery,[5,16,23–30] and the decision is made based on size, location, symptoms, and prior treatment. Conservative management is rarely used, but may be an option in elderly or debilitated patients, asymptomatic or with few symptoms, and small tumors.[15]

External radiation therapy has been used since the early 1950s for the treatment of GJT.[1] There is a recent publication of fractionated external radiation therapy in various types of head and neck paragangliomas, with an average follow-up of 4.1 years (range .1–22 years), using an average dose of 45 Gy in 25 sessions. This obtained tumor control at 5 years of 100% and 98.7% at 10 years. Of 66 patients treated for 81 paragangliomas, at least 68% had grade 1 and 2 acute toxicity, and 13% grade 3 acute toxicity requiring hospitalization. Thirty percent had grade 1 and 2 late toxicity (xerostomy). There were also 3 patients with grade 3 toxicity (carotid artery stenosis, middle cerebral artery in 75%, and necrosis of the temporal bone). In addition, the authors reported the presence of 2 radioinduced tumors: meningiomas. No patient had grade 4 toxicity.[31]

A long-term follow-up study[32] conducted in Prague, Czech Republic, studied 46 patients with GJT treated with Gamma Knife from 1992 to 2003. The age ranged from 21 to 79 years (median 56 years). Radiosurgery was the primary treatment in 17 patients (37%). Other treatments were open surgery followed by radiosurgery (46%), embolization (17%), and conventional radiotherapy (4%). The dose ranged from 10 to 30 Gy (median 20 Gy). Neurologic symptoms improved in 19 (42%) patients and deteriorated in 2 (4%). Lesions decreased in size in 34 (77%) patients and global tumor control was 98%. Only 1 patient had tumor growth and required retreatment at 182 months.

One of the major uncertainties and the main argument against the treatment of GJT with radiosurgery has been the lack of long-term results due to short follow-up. Given the slow growth of the tumor and that GJT are usually indolent, this study only included patients with a clinical and neuroimaging follow-up above 18 months, allowing us to have valuable information about the tumor and symptomatic control of patients undergoing radiosurgery. We found that the treatment achieved high disease control with tumor and symptoms control of 97% with a rate of acute toxicity less than 15% (all grade 1) and no patient experiencing late side effects. Therefore, our findings suggest that radiosurgery appears to be an effective and safe therapeutic option in patients with GJT.

Several publications focused on upfront surgery, recommending attempt at resection despite perioperative complications.[17,19,20,33] Ramina et al.[19] reported a study including 134 patients with tumors of various types in the jugular foramen; 16 had CN involvement (12%) and in 12 patients the damage was permanent (8.9%), 7 (4.5%) presented CSF fistula, 4 had meningitis (3%), 1 a hemiparesis, 1 a large symptomatic cervical hematoma, and 3 died in the perioperative period (3%). The authors report that compromise of the CN is the main complication and that it could lead to aspiration, pneumonia, and septicemia. Other large series presented similar results, never free from complications.[17,33] In this respect, we found a statistically significant association between patients having 1 CN involvement before radiosurgery and a higher risk of lack of improvement of symptoms. It is widely known among neurosurgeons that GJT surgery is a highly difficult process with significant complications and associated morbidity and mortality despite major surgical anesthesia and advances, the use of preoperative embolization, and intraoperative neurophysiologic monitoring. The location of the tumor, its high vascularity, and the presence of adjacent cranial and cerebral vessels make the process a challenge. In the present series, all patients who were previously treated surgically (15 of 29) had postoperative neurologic deterioration due to CN damage, which confirms that this procedure has substantial morbidity. Another alternative is performing the maximum possible resection followed by adjuvant radiation to the remnant tumor. This method is recommended in large lesions with mass effect. It allows tumor debulking favoring radiation treatment and reducing the possibility of damage to neural structures such as CN.[34]

Because of the inherent flaws in a retrospective study, confounding variables may exist that were not accounted for in this study. Moreover, considering patients were not prospectively followed up, selection bias and loss to follow-up might contribute to an underestimation of the toxicity. Despite the above limitations, as there are few data available concerning long-term outcome after the use of radiosurgery in GJT, the present study provides interesting information in this setting.

In conclusion, radiosurgery is an effective and safe treatment option for the management of primary or secondary GJT, achieving high tumor and symptoms long-term control with very low late toxicity. Based on current data, considering the high effectiveness with low toxicity of radiosurgery in the treatment of GJT, contrasted with technical difficulties and complications that may occur with surgery, the global trend is radiosurgery as the primary treatment of these tumors, leaving surgery for severe cases of symptomatic mass effect that require rapid decompression.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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