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Treatment Outcomes for Single Modality Management of *Glomus Jugulare* Tumors with Stereotactic Radiosurgery

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Abstract

Objectives—The objectives were to evaluate the audiological outcomes, response of symptoms, and response of tumor volume in patients with glomus jugulare tumors treated solely with single fraction gamma knife radiosurgery.

Study Design—Single institution retrospective review.

Setting—Academic, tertiary referral center.

Patients—The diagnosis code for glomus jugulare was used to identify patients. Only those who underwent gamma knife radiosurgery were included. Those previously treated with any modality were excluded. A total of 12 patients were included for the tumor response and symptom response data and 7 of those were included in the audiometric analysis.

Main Outcomes Measures—Audiometric data at most recent follow up compared to presentation, subjective improvement in pulsatile tinnitus, and change in tumor volume at most recent follow up compared to pretreatment.

Results—The average time to most recent follow up was 27.6 months. There was no significant change in pure tone average or word recognition. Pulsatile tinnitus completely resolved or improved in 80% of patients. Cranial neuropathies were stable or improved. A single patient experienced facial nerve paresis 2 years after treatment, which resolved with steroid treatment. Tumor control was 100% and the average change in tumor volume was a decrease of 37%.

Conclusion—Single modality Gamma Knife radiosurgery treatment of glomus jugulare tumors appears to be safe. Treatment results in decreased tumor volume and improved pulsatile tinnitus in most patients. There was no significant progression of hearing loss after treatment. Lower cranial nerve function remains stable in all patients.

Keywords

Stereotactic radiosurgery; *Glomus jugulare*

Introduction

The glomus tumor is the most common tumor of the middle ear and the second most common tumor found in the temporal bone.¹ Grossly, they appear reddish, vascular, and lobulated. They are a subtype of a larger group of tumors called paragangliomas which are derived from catecholamine-secreting chemoreceptor cells. Symptoms of palpitations, sweats, flushing, hypertension, and headaches are present in 1–3% of patients with these tumors.² Paragangliomas of the head and neck are categorized by their anatomic location along the parasympathetic nervous system. Carotid body tumors are located at the carotid bifurcation. *Glomus vagale tumors* present extracranially in close proximity to cranial nerve 10 with extension into the skull base. *Glomus jugulare* tumors (GJT) arise from the jugular bulb and involve the jugular foramen. *Glomus tympanicum* tumors arise from the promontory within the middle ear along Jacobson's nerve. Patients present with a range of symptoms depending on the location, catecholamine secretion, and size of the tumor. For the tumors involving the temporal bone, unilateral pulsatile tinnitus is the most common presenting symptom. Other symptoms include otalgia, hearing loss, dysphagia, dysphonia, vertigo, and headache, depending on tumor extension.

There are multiple options for treatment of GJT. Gross resection has been the mainstay of therapy but can be complicated by cranial neuropathies and significant surgical blood loss.^{3–6} Embolization is frequently utilized to minimize intra-operative blood loss. Multimodality therapy combining subtotal resection with various forms of radiotherapy has been shown to be effective at controlling tumor growth; however, surgical and radiation-induced complications still exist.^{6–13} Stereotactic radiosurgery (SRS) has been used successfully to treat GJT with potentially higher rates of tumor control. Decreased patient morbidity with lower rates of post-treatment cranial nerve dysfunction compared to surgery or fractionated radiotherapy have also been observed with SRS.^{6,12,14–17} The effect of different treatment modalities on cranial nerves and functional hearing outcomes is essential in the management of GJT and many reported series have solely focused on those managed with a multimodality approach. Furthermore, data regarding assessment of auditory function has not been reported using accepted reporting guidelines.¹⁸ The purpose of this study is to report the treatment outcomes of single modality SRS using the Gamma Knife radiosurgery (GKRS) unit in a cohort of patients with *glomus jugulare* tumors.

Methods and Materials

Patients

Institutional review board approval of the protocol was obtained prior to initiating the study (protocol 15-0031-P3H). Inclusion criteria included patients with radiographic evidence of GJT, single dose GKRS treatment, and at least 1 year of follow-up. Patients with embolization, surgical intervention, or other radiation treatment prior to GKRS were

excluded from the study. All patients were identified from the Departments of Otolaryngology, Neurosurgery, and Radiation Medicine. All patients were diagnosed by MRI skull base with contrast. Following treatment, patients were evaluated on an annual basis with surveillance imaging in the form of MRI or CT scan. The standard radiosurgery response classification was used to assess treatment outcomes (i.e. Grade I – volume decrease greater than 10%, Grade II – no growth, Grade III – tumor growth).¹⁹

Stereotactic Radiosurgery Treatment Planning

All patients identified received treatment using Stereotactic Radiosurgery at the University of Kentucky between 1999 and 2013. Patients who received treatment between 1999 and 2003 completed treatment on the Elekta Model AB, those receiving treatment between 2003 and 2008 on the Gamma Knife Model C, and from 2008 to current, treatments were on the Perfexion unit. All GKRS treatments were delivered as a single fraction. Patients underwent consultation with the surgeon (Neurosurgeon or Neurotologist), radiation oncologist, and medical physicist prior to treatment. Patients were deemed eligible for SRS if the largest dimension was less than 4cm. One patient had a tumor measuring 4.5cm in cranial-caudal dimension and after multidisciplinary team discussion; we elected to proceed with SRS. Patients with tumors greater than 4cm in the largest dimension generally are treated with external beam fractionated radiation. The treatment protocol involves standard stereotactic headframe placement with 4-point pin fixation. Stereotactic headframe measurements are then obtained and the patient then undergoes a MRI of the brain with and without contrast using a stereotactic MRI protocol. All images were acquired in the axial, sagittal, and coronal planes using 1mm cuts through the area of interest. The MRI images undergo quality assurance checks. The tumor is outlined by hand on each axial image on the treatment-planning computer. Tumor volume is calculated by the computer using the outlined images. Maximal linear anterior-posterior, cranial-caudal, and medial-lateral dimensions are also recorded. For the purpose of this study, pre-treatment and post-treatment volumes were calculated using an equation for ellipsoid volume using these 3 measurements. Treatment planning was performed at the time of MRI acquisition with the Leksell localization head frame in place. Planning was performed to generate radiation plans targeting the relevant isodose line encompassing the lesion, which most commonly was the 50% isodose line. Plans consisted of a mixture of shots using 4, 8, or 16mm collimators. The treatment dose varied between 12–18 Gy depending the tumor size and location with an attempt to minimize the radiation dose to the brainstem and other sensitive structures (i.e. – cochlea). The treatment plan was approved by the surgeon, radiation oncologist, and the medical physicist and then delivered with constant supervision of these providers. Following treatment delivery, the stereotactic head frame was removed and patients were discharged to home.

Audiometric and Cranial Nerve Testing

Available audiometric data was recorded in the form of pure tone average and word recognition scores. The clinic evaluation at the time of presentation was used to determine the presence of subjective hearing impairment, pulsatile tinnitus, vestibular symptoms, dysphagia, dysphonia, facial palsy, shoulder and tongue weakness. The most recent follow up clinic note was used to determine the post-treatment symptom presence.

Results

From 1999 until 2013, a total of 14 patients were treated with single modality GKRS. Demographic data and treatment parameters are outlined in Table 1. Two patients were lost to follow-up within the first year and were excluded from this review. There were 4 males and 8 females with an average age of 62.8 (31–77) years. The distribution was fairly even with 7 patients having a left-sided tumor and 5 having a right-sided tumor. The average length of follow-up was 27.6 (13–96) months after treatment with about half of patients still undergoing annual surveillance. Tumor control was 100% (83% Grade I, 16.7% Grade II). There was no progression of tumor growth in any of the patients and no patients required further intervention. The average change in tumor volume from treatment to most recent follow up was a decrease of 37% (0.8–77%). Specific patient treatment characteristics are included in Table 2.

Pre and post-treatment audiometric analysis was available in 7 patients. Figures A and B display the pre- and post-treatment pure tone average and word recognition scores in the affected ear. Sudden sensorineural hearing loss was a presenting symptom in 8.3% (n=1) of subjects. Subjective hearing loss in the affected ear was a complaint pre-treatment in 50% (n=6) of patients. A subjective decrease in hearing following radiosurgery was found in 25% (n=3) of patients. Tinnitus outcomes are included in Table 3. All patients except 2 (83.3%) had unilateral, pulsatile tinnitus on presentation. A decrease or complete resolution of the pulsatile tinnitus was found at most recent follow up in 8 out of the 10 patients who originally had that complaint. No patients developed or had worsening of pulsatile tinnitus after treatment.

The presence of other symptoms and cranial nerve involvement is presented Table 4. None of the patients presented with facial paresis or paralysis prior to treatment. There were no patients with facial paralysis and only 1 patient that developed facial paresis (grade III/VI) approximately 2 years after treatment that resolved with steroid medical management. Dysphagia and/or hoarseness were primary complaints in 33.3% of patients (n=4). Ipsilateral vocal fold paralysis was found in 25% (n=3) of these patients. These patients underwent subsequent injection laryngoplasty or vocal fold medialization. None of the patients with intact 10th cranial nerve function went on to develop dysphonia after treatment. Shoulder weakness (cranial nerve XI dysfunction) was a primary complaint in 16.7% of patients (n=2). Tongue weakness and atrophy of the ipsilateral hemi-tongue (cranial nerve XII dysfunction) was found in 8.3% (n=1) of patients. All patients with lower cranial nerves dysfunction subjectively reported that their symptoms were stable at most recent follow up. No patients had significant improvement in the dysfunction of cranial nerves VII, IX, X, XI, and XII.

Discussion

Although these tumors are typically slow-growing, the natural history of GJT poorly understood. Several treatment methods of GJT have been described including observation, surgery, external beam radiation therapy, and GKRS. The risk for malignant potential is low in GJT at 2–4%.²⁰ The location of these tumors puts at risk several vital structures within the

skull base thereby complicating effective treatment. This raises the question of how to achieve control of tumor growth while avoiding patient morbidity. It is important to understand that treatment efficacy of SRS is the absence of further tumor progression, which may gradually regress but almost never completely disappears. The total absence of tumor, and hence a cure, could only be obtained with surgery. The non-surgical treatment has been studied over the last 15–20 years, and GKRS and radiotherapy have demonstrated a decrease or stability of tumor size. Fractionated radiotherapy has side effects/complications similar to those seen in other head and neck tumors treated with radiotherapy including osteoradionecrosis, xerostomia, dermatitis, alopecia, serous otitis media, and external otitis.^{15,16} Therefore, radiosurgery has emerged as a modality to control tumor growth while limiting the complications of traditional radiation. The size of the tumor may influence the modality of treatment as tumors larger than 4 cm in greatest dimension begin to affect treatment planning such that obtaining a highly conformal treatment plan using SRS becomes limited, and therefore will likely require fractionated radiation. On average, the decrease in size of tumors treated in our study was 37% is comparable to other centers that have studied tumor response to GKRS.^{9,12,17,21–25} These are slow growing tumors and it is important to follow these tumors over longer periods of time to assess for control of growth.

There is a gap in the literature regarding the prognosis of cranial nerve function after non-surgical single modality management of GJT. In general, patients either maintain function of their cranial nerves or have improvement in their dysfunction after treatment but many of these studies included patients treated with multiple types of surgical and/or radiation treatment types.^{6,12,13,22–26} Our study demonstrated overall stability of cranial nerve function using single modality GKRS. Those with lower cranial neuropathies were rehabilitated well (i.e. - injection laryngoplasty, physical therapy). There were no reports of weight loss, recurrent pneumonia, or percutaneous gastrostomy tube placement for this group of patients after treatment. The one patient that developed a facial paresis after treatment returned to normal function after treatment with steroids resulting in a 100% rate of stability in cranial nerve dysfunction.

A study by Gandia-Gonzalez, et. al. reported an overall resolution of tinnitus in 54% of patients treated with GKRS (with or without other previous treatment methods) for GJT.¹⁷ Our study demonstrated that 80% of subjects reported either a complete resolution or decrease in pulsatile tinnitus. This is intuitive, considering the radiographical decrease in tumor volume in most patients, and will need long-term follow to assess for true treatment effectiveness. The mechanism behind this finding is unknown; however, other hypothetical mechanisms behind tinnitus resolution independent of overall tumor size include decrease in the overall vascularity of the tumor, decrease in turbulent flow within the tumor, and fibrosis of the segment of the tumor adjacent to the ossicles. Further investigation with long-term follow-up of this finding is warranted.

The cochlear dose of radiation has been studied in treatment of vestibular schwannoma and the dose beyond which serviceable hearing deteriorates is 3.0 – 5.3 Gy.^{27–29} A review of patients treated with GKRS for vestibular schwannoma and GJT at the Mayo Clinic estimate the rate of preservation of serviceable hearing at 1 and 3 years respectively to be 80 and 55%.³⁰ Subjectively, 3 patients complained of worsening hearing after treatment while 1

patient reported improved hearing. Sensorineural hearing loss was the main component of hearing loss in our patients with 2 patients having a mixed hearing loss. We do not know if the hearing loss observed before treatment was due to tumor growth, so it is difficult to conclude that controlling tumor growth will prevent further hearing loss. Yet, the fact that there was no significant decline of hearing in our patients suggests that control of the tumor growth prevented any further hearing loss that was caused by tumor effect. All analysis of hearing took place at least 13 months after treatment, so deterioration of hearing was not seen to be an early side effect of GKRS. Long-term follow-up is warranted to assess delayed treatment effects on hearing.

This study, similar to other GKRS studies on GJT, is limited by sample size. Most other studies include other forms of radiation therapy (i.e. – fractionated, CyberKnife, and linear accelerator)³¹ or include patients with previous surgical management or embolization. The relative homogeneity of the study population strengthens the study in the face of limited study size. Although all patients were followed for at least one year, the length of follow-up is a limitation to this study. Considering the growth rate of these tumors, longer-term follow-up is necessary to determine the effectiveness of GKRS in long-term growth control and prevention of functional decline. The retrospective format also represents a limitation of the study. Certainly single modality treatment of these tumors is dependent on multiple factors (size, location, underlying cranial neuropathies) and other modalities play a key role in the management of these tumors. Further prospective research is needed to assess effectiveness of GKRS in the treatment of patients with GJT. This should be combined with quality of life data as this information is also lacking in the field.

Conclusions

Single modality Gamma Knife radiosurgery treatment of glomus jugulare tumors appears to be safe and efficacious. We observed 100% growth control rate (decrease in tumor volume of at least 10% in 83.3%) and a decrease in pulsatile tinnitus in 80% of symptomatic patients. There was no significant progression of hearing loss after treatment. Lower cranial nerve function remains stable in all subjects. Long-term follow-up and quality of life research is warranted to assess the value of GKRS as a single mode of treatment for select patients.

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Figure B.
Post-treatment audiometric data of the affected ear

Table 1

Demographics and Treatment Parameters

	Value	Range
Age at treatment, mean	62.8	31–77
Gender, % male	33	-
Tumor location, % right	41.7	-
Most recent follow up, months, mean	27.6	13–96
Specialty		
Otolaryngology	7	-
Neurosurgery	5	-
Tumor volume at treatment, mL, mean	8.42	2.3–23.2
Tumor volume at follow-up, mL, mean	4.62	1.1–9.9
tumor volume, %, mean	37	0.8–77
Marginal dose, Gy, mean	15.5	12–18
Marginal dose, Gy, median	15	12–18
Max dose, Gy, mean	31.25	25–36
Isodose line, %, mean	50.83	50–60
Isocenters, #, mean	12.17	2–20

TABLE 2

Patient characteristics

	Pre-GKRS volume (cm ³)	Post-GKRS volume (cm ³)	Fisch classification	Radiation dose (Gy)	Isodose line (%)	Volume Decrease (%)
Subject 1	3.16	2.31	C	15	50	26.9
Subject 2	5.65	3.78	C	15	50	33.1
Subject 3	4.75	4.71	C	15	50	0.84
Subject 4	4.27	1.12	C	15	60	73.8
Subject 5	9.74	5.03	C	15	50	48.4
Subject 6	2.41	1.64	C	15	50	29
Subject 7	6.53	4.97	C	16	50	23.9
Subject 8	6.07	5.72	C	16	50	5.8
Subject 9	10.37	7.29	C	18	50	29.7
Subject 10	16.48	9.9	C	16	50	39.9
Subject 11	8.56	3.76	C	18	50	56.1
Subject 12	23.23	5.23	D1	12	50	77.5

TABLE 3

Pulsatile tinnitus response to treatment(%)

Total	No change	Improved	Resolved
10 patients	2 (16.7)	4 (40)	4 (40)

TABLE 4

Symptoms and Cranial Nerve Involvement (%)

	Pre-GKRS	Post-GKRS
Imbalance	5 (41.7)	5 (41.7)
Subjective hearing loss	6 (50)	6 (50)
CN 7, face weakness	0 (0)	1 (8.3)
CN 9, dysphagia	1 (8.3)	1 (8.3)
CN 10, dysphonia	3 (25)	3 (25)
CN 11, shoulder weakness	2 (16.7)	2 (16.7)
CN 12, tongue weakness	1 (8.3)	1 (8.3)