Gamma Knife radiosurgery for glomus jugulare tumors: a single-center series of 75 cases

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OBJECTIVE Glomus jugulare tumors are rare indolent tumors that frequently involve the lower cranial nerves (CNs). Complete resection can be difficult and associated with lower CN injury. Gamma Knife radiosurgery (GKRS) has established its role as a noninvasive alternative treatment option for these often formidable lesions. The authors aimed to review their experience at the National Centre for Stereotactic Radiosurgery, Sheffield, United Kingdom, specifically the long-term tumor control rate and complications of GKRS for these lesions.

METHODS Clinical and radiological data were retrospectively reviewed for patients treated between March 1994 and December 2010. Data were available for 75 patients harboring 76 tumors. The tumors in 3 patients were treated in 2 stages. Familial and/or hereditary history was noted in 12 patients, 2 of whom had catecholamine-secreting and/or active tumors. Gamma Knife radiosurgery was the primary treatment modality in 47 patients (63%). The median age at the time of treatment was 55 years. The median tumor volume was 7 cm³, and the median radiosurgical dose to the tumor margin was 18 Gy (range 12–25 Gy). The median duration of radiological follow-up was 51.5 months (range 12–230 months), and the median clinical follow-up was 38.5 months (range 6–223 months).

RESULTS The overall tumor control rate was 93.4% with low CN morbidity. Improvement of preexisting deficits was noted in 15 patients (20%). A stationary clinical course and no progression of symptoms were noted in 48 patients (64%). Twelve patients (16%) had new symptoms or progression of their preexisting symptoms. The Kaplan-Meier actuarial tumor control rate was 92.2% at 5 years and 86.3% at 10 years.

CONCLUSIONS Gamma Knife radiosurgery offers a risk-versus-benefit treatment option with very low CN morbidity and stable long-term results.

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KEY WORDS glomus tumor; Gamma Knife; stereotactic radiosurgery; oncology

GLOMUS jugulare and tympanicum tumors are also known as skull base nonchromaffin paragangliomas and chemodectomas. They arise from the chemoreceptor paraganglion cells, which are part of the parasympathetic system involved in autonomic regulation of respiration and blood pressure. The glomus jugulare tumor arises from paraganglion cells located in adventitia of the jugular bulb at the jugular foramen. The glomus tympanicum tumor arises from similar cells along Jacobson's nerve, the tympanic branch of the glossopharyngeal nerve, and Arnold's nerve, the auricular branch of the vagus nerve. Other possible locations within the middle ear are in relation to the tympanic canaliculus, the promontory, and the lesser petrosal nerve.

These tumors are rare highly vascular tumors with a reported incidence of 1 case per 1.3 million persons.³⁰ They represent 0.6% of all cranial neoplasms, with the glomus tympanicum tumor being the most common neoplasm of the middle ear.^{33,43} Most of these tumors are benign but locally destructive with an estimated growth rate of 1 mm per year.³⁸ Rare malignant variants (1%–5%), which can metastasize, have been reported.⁴⁷

These tumors are most common in females in the 5th and 6th decades.^{18,34,57} Presentation at an earlier age in the 3rd decade suggests an underlying genetic mutation of the succinate dehydrogenase (SDH) enzyme with the potential for malignant or aggressive behavior, metastasis, and multicentricity.³⁴

ABBREVIATIONS CN = cranial nerve; CSF = cerebrospinal fluid; GKRS = Gamma Knife radiosurgery; GTR = gross-total resection; RT = radiotherapy; SDH = succinate dehydrogenase; SDHB = SDH enzyme complex subunit B.

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Clinically, patients most commonly present with pulsatile tinnitus, hearing loss, and lower cranial nerve (CN) deficits. Other symptoms are dizziness and localized pain. Presentation with facial nerve weakness occurs rarely and indicates an infiltrative tumor.^{1,4,41} Large tumors can have significant intracranial and extracranial extensions involving vascular structures of the carotid sheath and causing brainstem compression. Histologically, the tumors are similar to pheochromocytomas, and although the majority are nonfunctioning, they secrete catecholamines in 1%–3% of cases, in which patients may present with symptoms of catecholamine hypersecretion such as hypertension, tachycardia, palpitation, headache, and anxiety.^{22,34}

Traditionally, these tumors were resected, but because of their high vascularity and the frequent involvement of the lower CNs, surgery entails significant risk. Whereas microsurgical removal still constitutes a valuable therapeutic option, particularly for giant tumors with significant brainstem compression, in recent years there has been a noticeable shift to treat these lesions with a less invasive treatment, namely radiation. Gamma Knife radiosurgery (GKRS) has been increasingly popular in treating these lesions given its high precision and the sparing of nearby critical structures from the radiation field, with reported successful outcomes. We present a retrospective single-center series of cases treated at the stereotactic radiosurgery center in Sheffield, United Kingdom.

Methods

The National Centre for Stereotactic Radiosurgery database was retrospectively reviewed in 2012 for treated cases of glomus jugulare and tympanicum tumors over a 16-year period between March 1994 and December 2010. No cases were included after this period to allow for sufficient follow-up. The medical notes, procedural details, and most recent clinical and MRI follow-up data were collected and analyzed. When data were deemed not up to date, the most recent clinical and radiological follow-up was actively requested from the referring hospitals. The Royal Hallamshire Hospital Review board approved the study protocol.

Patient Characteristics

Of 83 total patients, 8 were lost to follow-up with incomplete data. Seventy-six tumors were separately analyzed in the remaining 75 patients, with 1 patient having bilateral tumors (Fig. 1). The patient cohort consisted of 35 males and 40 females. Median age at the time of treatment was 55 years (range 21–84 years). The tumor was on the left side in 40 patients and on the right in 34 patients, and 1 patient had bilateral tumors. This latter patient had been referred after biopsy of a mass in the left ear canal with histology confirming a paraganglioma. Subsequent genetic analysis revealed an SDH enzyme complex subunit B (SDHB) mutation.

A familial paraganglioma history was noted in 12 patients, among whom a hereditary mutation of the mitochondrial SDH enzyme complex mutation deficiency was found in 7 cases after genetic analysis. An SDHB mutation was confirmed in 5 patients and a subunit C (SDHC)

FIG. 1. Axial (left) and coronal (right) post-gadolinium MR images obtained in a patient with bilateral glomus jugulare tumors. A biopsy from the left ear confirmed the diagnosis. Subsequent genetic analysis revealed an SDH enzyme mutation subtype B (SDHB). The tumors were stationary in size after 24 months of radiological follow-up.

mutation in 2 patients. Two patients had endocrinologically active tumors secreting catecholamine (raised urinary vanillylmandelic acid). Patient characteristics and duration of follow-up are summarized in Table 1.

Among the 75 patients, GKRS was the primary treatment modality in 47 patients (63%), 14 (18.7%) of whom had been referred after tumor growth was observed on repeat imaging. Twenty-four patients (32%) had undergone prior resection; 1 of these 24 patients had received preoperative radiotherapy (RT) as well, and another patient had undergone a postoperative embolization procedure. Three patients (4%) underwent embolization only and 1 patient (1.3%) received only RT prior to the radiosurgery.

In 50 patients the diagnosis was based on clinical presentation (tinnitus, hearing loss, associated CN deficits), MRI characteristics (increased T2-weighted signal intensity, decreased T1-weighted signal intensity, and intense enhancement after gadolinium administration), and additional information from CT and cerebral angiography.

Hearing loss (CN VIII) was the most common presenting symptom (63 patients [84%]), followed by pulsatile tinnitus in 50 patients (66.7%). Twenty-eight patients (37.3%) presented with ataxia. The frequency of other CN deficits before GKRS treatment and not attributed to a post-resection deficit were as follows: CN V, 11 patients (14.6%); CN VI, 1 patient (1.3%); CN VII, 13 patients (17.3%); CN IX, 22 patients (29.3%); CN X, 25 patients (33.3%); CN XI, 10 patients (13.3%); and CN XII, 20 patients (26.7%). Most patients had more than 1 CN deficit, and various lower CN deficit combinations were observed in 30 patients (40%; Table 2).

Among the 24 patients (32%) who had undergone prior resection, 10 had sustained a postoperative CN deficit associated with either a single nerve or a combination of nerves. The most commonly noted postoperative deficits were those associated with CN VII in 7 patients, followed by CN X in 6 patients (transient vocal cord paresis that improved prior to GKRS in 1 patient), CN IX in 4 patients, CN VIII in 2 patients, and CNs V, XI, and XII in 1 patient each. None of these patients later showed any

TABLE 1. Summary of patient demographics and duration of follow-up

Parameter	Value
No. of patients	75
Median age in yrs (range)	55 (21–84)
M/F (no. [%])	35 (46.6)/40 (53.4)
Lesion side: lt/rt/bilat (no. [%])	40 (53.4)/34 (45.3)/1 (1.3)
Familial or hereditary lesion: proven/unproven (no. [%])	12 (16.0)/63 (84.0)
Histological confirmation: yes/no (no. [%])	25 (33.3)/50 (66.7)
Median radiological FU in mos (range)	51.5 (12–230)
Radiological FU in yrs (no. [%]): <5/5–10/>10	41 (54.6)/21 (28)/13 (17.4)
Median clinical FU in mos (range)	38.5 (6–223)
Clinical FU in yrs (no. [%]): <5/5–10/>10	46 (61.3)/21 (28)/8 (10.7)

FU = follow-up.

improvement in their preexisting deficits after GKRS, and 1 patient experienced transient worsening of preexisting CN VII dysfunction.

Radiosurgical Procedure

Leksell Gamma Knife Models S, C, 4C, and Perfexion (Elekta AB) were used to administer treatment over the specified timeframe. The Leksell stereotactic frame was affixed after a local anesthetic was applied, followed by the acquisition of thin 1-mm-slice MRI sequences (T1- and T2-weighted, fat suppression, and post-gadolinium T1-weighted). Gamma Knife radiosurgery dose planning was performed by a team comprising a neurosurgeon, neuroradiologist, and medical physicist. Seventy-six tumors were treated in 75 patients. The radiosurgery treatments were performed in a single session in 73 cases and as a 2-staged treatment in 3 cases. The radiosurgical treatment data parameters were analyzed in terms of individual tumors.

The median tumor volume was 7 cm³ (range 0.2–53.9 cm³). A median number of 11 isocenters (range 2–44) was used in dose delivery. The median tumor margin dose was 18 Gy (range 12–25 Gy) and was prescribed to the 50% isodose line (range 40%–56%) in 59 tumors (Table 3). After our initial experience in 13 cases treated using the Model S Gamma Knife during the first 7 years of the study period, we adjusted the protocol to deliver a significantly lower margin dose to the tumors. With technical improvements, a higher number of isocenters has also been used.

Clinical and Radiological Evaluation

Clinical outcome was assessed through neurological examination including CN function every 6 months for the first 2 years and on a yearly basis thereafter. The patients' neurological condition prior to GKRS treatment served as a baseline and after treatment was described as unchanged, improved, or worse, depending on whether there were new symptoms or progression of preexisting symptoms. Post-treatment complications were classified as transient or permanent. Tumor was typed according to the Glasscock-

TABLE 2. Presenting symptoms

Symptom	No. of Patients (%)
CN neuropathy prior to GKRS*	
V	11 (14.6)
VI	1 (1.3)
VII	13 (17.3)
VIII	63 (84)
IX	22 (29.3)
X	25 (33.3)
XI	10 (13.3)
XII	20 (26.7)
Lower CN (IX–XII) combinations	30 (40)
Tinnitus	50 (66.6)
Ataxia	28 (37.3)

* Not attributed to postsurgical deficit.

Jackson classification:³⁵ Type I (small tumor involving the jugular bulb, middle ear, and mastoid); Type II (tumor extending under the internal auditory canal); Type III (tumor extending into the petrous apex); and Type IV (tumor extending beyond the petrous apex into the clivus or infratemporal fossa). The Fisch classification was applied as well:⁵² Type A (tumor limited to the middle ear cleft); Type B (tumor limited to the tympanomastoid area); Type C (tumor involving the infralabyrinthine compartment of the temporal bone and extending into the petrous apex); Type D1 (tumor with an intracranial extension < 2 cm in diameter); and Type D2 (tumor with an intracranial extension > 2 cm in diameter). The number and percentage of tumors in each category are presented in Table 4. The ability to treat extensive tumors with downward extension into the cervical region is pertinent to GKRS. Hence, in addition to the above classifications, we categorized tumors according to their location and extent of caudal extracranial cervical tumor extension. After treatment tumors were classified by location after reviewing coronal post-gadolinium administration MR images: skull base (with no cervical extension), extracranial cervical extension to the upper border of the first cervical (C-1) vertebra, upper border of the second cervical (C-2) vertebra, or upper border of the third cervical (C-3) vertebra (Table 4).

The patients underwent radiological follow-up with T1-weighted, T2-weighted, and post-gadolinium T1-weighted MRI at 6-month intervals during the 1st year and then yearly thereafter. Where possible, contrast-enhanced T1 volume scans were used to generate a 3D tumor volume for comparison with the GammaPlan treatment volume measurements. In some cases follow-up imaging was performed at a remote center with protocols that differed from our own, in which case anteroposterior, lateral, and vertical diameters were obtained; a change greater than 2 mm was regarded as a real change in tumor size. After documented tumor control (stationary or decreased tumor size) and a satisfactory neurological condition (unchanged or improved) over a 5-year period, the imaging interval could be changed to 2 yearly scans in the majority of patients. All patients underwent regular periodic MRI examina-

TABLE 3. Gamma Knife radiosurgery treatment parameters

Parameter	Value
GKRS tumor margin dose in Gy	
Mean $\pm$ SD	18.3 $\pm$ 3.0
Median	18
Range	12–25
GKRS max dose in Gy	
Mean $\pm$ SD	37.2 $\pm$ 6.3
Median	36.7
Range	23.2–50
Prescription Isodose line in %	
Mean $\pm$ SD	49.6 $\pm$ 2.3
Median	50
Range	40–56
No. of isocenters	
Mean $\pm$ SD	12.1 $\pm$ 7.2
Median	11
Range	2–44
Tumor vol at GKRS in cm ³	
Mean $\pm$ SD	9.1 $\pm$ 8.5
Median	7.0
Range*	0.2–53.9
Treatment vol at GKRS in cm ³	
Mean $\pm$ SD	8.6 $\pm$ 6.4
Median	7.4
Range*	0.2–32.9

SD = standard deviation.

* Disparity in ranges due to incomplete coverage of tumors extending extra-cranially.

tions. Data from repeated clinical examinations were not always available, probably reflecting an absence of new symptoms. Thus, the median radiological follow-up was 51.5 months (range 12–230 months), whereas the median clinical follow-up was 38.5 months (range 6–223 months).

Statistical Analysis

Data were analyzed using the software package IBM SPSS version 22 (IBM Corp.). Univariate analysis was undertaken using the log-rank test for categorical data and Cox regression for continuous data, as appropriate. Variables identified with a $p < 0.1$ were included in a multivariate Cox proportional-hazards regression analysis to determine the independent predictors of radiological and clinical progression-free survival. Significance was accepted at $p < 0.05$. Hazard ratios and 95% confidence intervals were documented. A Kaplan-Meier survival analysis was undertaken to show the radiological progression-free survival. The variables included in the analysis were age, sex, prior treatment (surgery, embolization, or RT), familial history, Glasscock-Jackson and Fisch types, and tumor location (skull base vs extracranial cervical extension to the upper border of the C-1, C-2, or C-3 vertebra). The clinical variables included were presentations with tinnitus or lower CN deficit. The GKRS treatment variables selected were tumor volume, margin dose, maximal dose, and number of isocenters.

TABLE 4. Summary of tumor grades and location

Parameter	No. (%)
No. of tumors	76
Glasscock-Jackson type: I/II/III/IV	11 (14.5)/16 (21.1)/16 (21.1)/33 (43.4)
Fisch type: A/B/C/D1/D2	2 (2.6)/17 (22.3)/30 (39.4)/20 (26.3)/7 (9.2)
Tumor location: skull base/C-1/C-2/C-3	38 (50.0)/21 (27.6)/10 (13.1)/7 (9.2)

Results

Tumor Control

On the last follow-up MR images, 43 tumors (56.6%) had decreased in size, 28 (36.8%) tumors were unchanged, and 5 (6.6%) had increased in size. Thus, overall tumor control was achieved in 71 tumors (93.4%). Actuarial progression-free survival was 97.2%, 92.2%, and 86.3% at 2, 5, and 10 years, respectively (Fig. 2). Of the 5 growing tumors, 2 had salvage treatments, one with repeated GKRS and one with fractionated RT. The patients in the 3 remaining cases were still under observation for minimal increases in tumor size. This study included 13 patients whose follow-ups were longer than 10 years' duration; the tumors reduced in size in 10 of the patients and were unchanged in 3.

Previous treatment ($p = 0.060$) and extracranial cervical extension ($p = 0.077$) tended to be associated with poorer tumor control (Table 5). Specifically, 2 of the 5 cases with observed tumor growth had extracranial tumor extending below C-3, and the growth appeared to be outside the radio-surgically treated field. The Glasscock-Jackson and Fisch classifications (both of which describe the cranial extent of these tumors) were not related to outcome. Moreover, outcome was not related to tumor volume or prescribed dose. In this study, cases with a familial history or SDH mutation were not associated with poorer outcomes than cases of sporadic tumors. No dependent predictors reached statistical significance ($p < 0.05$) on the multivariate Cox regression statistical model for tumor progression-free survival.

With regard to the 2 catecholamine-secreting tumors noted in the present series, 1 case was published as a case report with a successful reduction in tumor volume in a 37-year-old female patient and the attainment of near-normal levels of urinary catecholamine excretion after 37 months.²² The second patient was a 60-year-old male patient who had presented with hearing loss, tinnitus, and facial numbness (CN V). Hypertension, atrial fibrillation, and anxiety had also been diagnosed. High levels of metanephrines and vanillylmandelic acid were detected in his urine. After 49 months of radiological follow-up after treatment, his tumor had reduced in size; his symptoms related to catecholamine hypersecretion tailored off on clinical follow-up as well (Fig. 3).

Clinical Outcome

Fifteen patients (20%) reported improvement in their

FIG. 2. Tumor progression-free survival after GKRS.

pretreatment symptoms, with the resolution of pulsatile tinnitus in 6 of the patients and hearing improvement in 3. Forty-eight patients (64%) reported their initial symptoms as unchanged. Twelve patients (16%) reported a worsening of clinical symptoms after treatment, but a new permanent CN deficit was noted in only 2 patients. In 1 of these patients the deficit was a vocal cord paresis, which was treated with speech therapy; in the other patient a partial facial nerve palsy developed. In both patients tumor growth was controlled. In the remainder of the patients, the CN morbidity was transient and onset occurred within 5–8 months after treatment. A transient new CN deficit (V, VII, X) was observed in 4 patients. Transient worsening of preexisting CN VII and CN X function was noted in 6 patients, with the facial nerve being the most commonly affected in 3 patients. These patients were prescribed a short (1–2 weeks) course of steroids (dexamethasone), which gradually helped restore CN function to pretreatment levels. Transient worsening of the more subjective symptoms of dizziness and unsteadiness was reported in 5 patients.

In this study, larger tumor volumes ($> 7 \text{ cm}^3$) were associated with an increased risk of CN damage ($p = 0.038$), and the presence of CN deficits before radiosurgery was associated with an increased risk of CN deficits after radiosurgery ($p = 0.027$). This was significant on both univariate and multivariate analysis (Table 6).

Five patients died of unrelated causes during the study period.

Discussion

Glomus jugulare tumors are rare and their management remains controversial as existing studies addressing the various treatment options are retrospective reports with a few systematic meta-analyses on each therapeutic modality.⁴³ The treatment options are resection, RT, stereotactic RT, radiosurgery, and continued observation or conservative management. Their treatment is becoming increasingly multidisciplinary, and several factors are taken into consideration during decision making: patient age, physical condition, tumor size, lesion growth rate, presenting symptoms and preexisting CN deficits, comorbidities, familial and/or hereditary history, and, in particular, the desires and expectations of patients regarding their functional outcome.

Traditionally, resection with adjunctive preoperative embolization constituted the mainstay of treatment aiming to achieve a “cure” by complete tumor removal. This therapeutic modality has proven difficulty and complexity due to the frequent lower CN involvement as these tumors are noted to infiltrate between the CN fascicles and perineurium with reactive fibrosis even when the nerves are still functioning,^{12,57} rendering complete resection occasionally impossible without sacrificing these nerves.⁶⁰ Moreover, preoperative embolization does not reduce the risk of new postoperative CN deficits⁴⁹ and in itself carries a risk of permanent cranial neuropathy because of the overlapping blood supply between these tumors and the CNs.^{25,26}

TABLE 5. Factors predictive of radiological tumor progression-free survival

Variable	HR	95% CI	p Value
Univariate analysis			
Age (≤ 55 vs > 55 yrs)	0.820	0.127–5.307	0.835
Male	0.821	0.136–4.949	0.829
Previous treatment	0.020	0.000–32.697	0.060
Hereditary lesion	1.390	0.155–12.452	0.768
Tinnitus	0.541	0.087–3.358	0.503
Lower CN deficit	2.271	0.376–13.705	0.358
Tumor vol (≤ 7 vs > 7 cm ³)	1.507	0.251–9.060	0.652
Margin dose (≤ 18 vs > 18 Gy)	0.670	0.111–4.025	0.659
Max dose	0.903	0.777–1.050	0.186*
No. of isocenters	1.047	0.931–1.177	0.445*
Glasscock-Jackson type	0.796	0.361–1.754	0.152
Fisch type	0.822	0.270–2.497	0.546
Location (intracranial vs extracranial extension to C-1, C-2, C-3)	1.636	0.741–3.612	0.077
Multivariate analysis			
Previous treatment	—	—	0.964
Location (intracranial vs extracranial extension to C-1, C-2, C-3)	2.040	0.801–5.199	0.135

— = could not be calculated given the low number of events.

* Cox regression.

In published surgical series,^{1,9,18,36,37,53,54,57,58,67,68} the results of total resection vary between 76% and 96%. Reported recurrence rates are between 7% and 10% with a median time to recurrence of 5.8 years in one study.³⁷ Rates of postoperative CSF leaks vary between 3.7%⁵⁸ and 17.6%,⁹ and rates of new postoperative lower CN deficits varied between 10%⁵⁷ and 47% in an early series by Jackson et al.³⁶ Mortality rates can be as high as 4.2%.⁵⁷ The surgical morbidity associated with damage to the lower CNs invariably requires early postoperative tracheostomy and feeding gastrostomy to prevent aspiration pneumonia, laryngeal injection for vocal cord paresis, and intensive postoperative rehabilitation.^{18,50,57} It was also noted that patients with large tumors will have some degree of preoperative vagal dysfunction with expected postoperative dysphagia.^{12,50}

Despite the significant surgical advances and intraoperative aids such as electrophysiological monitoring, surgical morbidity and mortality remained relatively high. In 2012 Makiese et al.⁴⁶ reported on a surgical series of 75 cases in which gross-total resection (GTR) was achieved in 78.7% of cases. The rates of lower CN deficits were 6.6%; CSF leak, 5.3%; and mortality, 2.7%.

There is, of course, the question of whether one should simply observe these tumors. However, they do grow, albeit at a very slow rate, and a watch-and-wait policy may increase the risks of subsequent interventions as the lesions gradually attain a larger size and infiltrate surrounding structures. Hence, conservative management is usually reserved for elderly patients or those who do not desire treatment.⁶⁴

To avoid and minimize the potential for iatrogenic CN

FIG. 3. Treatment planning axial (A) and coronal (B) post-gadolinium MR images, and follow-up (49 months posttreatment) axial (C) and coronal (D) post-gadolinium MR images.

injury with the resultant loss of quality of life and risk of mortality, there has been a noticeable paradigm shift to instead perform a function-preserving subtotal resection aimed at achieving a satisfactory and safe decompression, followed by postoperative RT,^{18,66} GKRS,^{38,39,52} or a watch-and-wait policy for tumor remnants. This strategy has been recommended particularly for large complex tumors and, by some authors, for elderly patients.^{15,69} Fortunately, the occurrence of large tumors with significant brainstem compression and dural invasion remains relatively rare and even more so in recent years because of earlier radiological diagnosis.^{1,12}

Glomus tumors are considered to be relatively radiosensitive,¹⁴ and radiation treatment modalities aim to arrest tumor growth and achieve local tumor control. Among these modalities, GKRS has emerged as an attractive minimally invasive treatment with an established role for more than 2 decades. The main advantages are its high precision with frame application and dose delivery to a prescribed tumor volume with a steep dose drop-off resulting in negligible radiation toxicity and CN morbidity.^{31,43} In addition, it is performed in a single treatment session, although staged treatments can be performed for larger tumors. GKRS has been increasingly indicated as a primary treatment, as well as a salvage treatment for residual and recurrent tumors after previous resection.

In all published GKRS studies, there were essentially no cases of treatment-related mortality and very low CN morbidity, cases of which were mostly temporary. The lower CNs have been noted to tolerate a radiation dose of up to 25 Gy, although transient radiation-induced CN neu-

TABLE 6. Factors predictive of clinical progression-free survival

Variable	HR	95% CI	p Value*
Univariate analysis			
Age (≤ 55 vs > 55 yrs)	2.058	0.570–7.431	0.262
Male	2.381	0.686–8.265	0.160
Previous treatment	0.563	0.149–2.135	0.392
Hereditary lesion	1.597	0.418–6.108	0.490
Tinnitus	0.420	0.110–1.607	0.193
Vertigo	0.596	0.157–2.255	0.441
Lower CN deficit	3.865	1.118–13.360	0.022
Tumor vol (≤ 7 vs > 7 cm ³)	4.810	1.034–22.373	0.027
Margin dose (≤ 18 vs > 18 Gy)	0.444	0.128–1.535	0.188
Max dose	0.937	0.853–1.028	0.169†
No. of isocenters	1.062	0.976–1.156	0.163†
Glasscock-Jackson type	2.740	0.946–7.935	0.221
Fisch type	2.584	0.911–7.329	0.337
Location (intracranial vs extracranial extension to C-1, C-2, C-3)	1.684	0.990–2.864	0.191
Multivariate analysis			
Tumor vol	5.129	1.092–24.092	0.038
Lower CN deficit	4.175	1.181–14.755	0.027

* Boldface type indicates statistical significance.

† Cox regression.

ropathy can occur with lower doses.⁵⁹ Early and midterm GKRS reports were encouraging with reported tumor control rates of 100% across 11 studies^{7,16,19–21,24,42,45,59,61,62} and over 94% in 2 studies over a median duration of 3.5 years of follow-up.^{27,55} Only 3 studies reported tumor control rates below 90%.^{13,39,65} Because of an observed growth rate of 0.8 mm per year and a tumor doubling time of approximately 10 years (median 4.2 years),³⁸ these earlier reports and later reviews recommended longer follow-ups to establish whether tumor control is maintained.⁴⁰ Two preliminary studies were performed by Eustacchio et al.¹⁷ and Gerosa et al.²⁸ with tumor control rates of 95% over a median follow-up longer than 4 years.

Studies with longer follow-up intervals have been published, confirming maintained tumor control against the natural history of the disease. The largest study to date, performed under the auspices of the North American Gamma Knife Consortium, is the multicenter analysis by Sheehan et al.⁶³ in which 132 patients were followed up for a median duration of 4.2 years and in whom overall tumor control was 93%. Improvement in preexisting CN deficits was observed in 11% of patients, and new or progressive CN deficits were noted in only 15%, with no deaths. More recently, 2 additional retrospective series reported tumor control rates of 95% and 94.8% over a median follow-up of 9.8 years and a mean follow-up of 7.2 years, respectively.^{23,44} Gamma Knife radiosurgery studies are summarized in Table 7.

The current study contributes to the literature by confirming stable long-term results after GKRS. The overall rate of tumor control was 93.4% over a median follow-up of 51.5 months. We observed a new CN deficit in only 2

patients. The outcome rates are better and the CN complication rates are far lower than those following surgical treatment and with much less of an impact on patient quality of life. In the future, better imaging with more complex plans utilizing a greater number of isodose centers may further improve results in terms of CN morbidity, as now we would routinely identify the facial nerve and plan around this.

There are issues in terms of tumor size and extent. Our results suggest specifically that there may be more CN morbidity for larger tumors and that tumors with a greater caudal extent may have poorer control rates. These observations may justify earlier intervention. Our study supports the findings of previous authors that the surgical classification types of Glasscock-Jackson and Fisch have no correlates with outcome after GKRS.^{59,63} Because glomus jugulare tumors spread into the path of least resistance, they can potentially extend downward along the carotid sheath.⁵⁶ This caudal extension may be a limiting factor in the efficacy of GKRS due to the target reach ability of some specific Gamma Knife models as experienced in our series; however, evolving platforms for delivering radiosurgery treatments may allow this issue to be better addressed in the future.

The genetic predisposition of these tumors has been an adverse prognostic factor, with hereditary and/or familial forms tending to occur at an earlier age, presenting as bilateral disease, exhibiting aggressive behavior, having high recurrence rates, and having an association with pheochromocytoma.⁶ Up to 30% of paragangliomas are genetically determined by loci on chromosomes 11q and 1q^{6,10} with mutations in 6 susceptibility genes of the mitochondrial enzyme complex II, which behave like tumor suppressor genes, identified: SDHD,⁵ SDHB,³ SDHC,⁵¹ SDHA,¹¹ SDHAF2,³² and VHL.⁸ The aggressive variant with metastatic potential had been linked to the SDHB subtype, which was prognostic for malignant behavior, recurrence, and risk of death in one multicenter study.^{2,10} But while these factors may affect the natural history of the disease, in the present study, they did not negatively impact the clinical results achieved. In the subgroup of 12 patients (16%) in which a familial history of paraganglioma was identified and all patients were alive at the date of their last follow-up, tumor control was observed in all except one patient with an SDHB mutation who had developed “out of the radiation field” growth from an extracranial cervical extension of the tumor. The patient subsequently underwent repeat GKRS for the entire tumor volume resulting in later volume reduction.

No factors correlating with tumor progression-free survival were identified on statistical analysis; however, the absence of lower CN involvement at presentation and a tumor volume less than 7 cm³ correlated with a greater likelihood of either an improvement or no progression of symptoms.

The disadvantages of this study are its retrospective nature and the fact that its data were obtained from a single center. We acknowledge that because some patients were not followed up locally, the possibility of variation in follow-up data is introduced; however, the variables recorded for patient follow-up were standardized.

Of note, similar good control rates have been reported

TABLE 7. Summary of published GKRS studies

Authors & Year	No. of Patients	Margin Dose (Gy)	FU (mos)	Tumor Control Rate	Rate of Clinical Deterioration Reported Post-GKRS (transient & permanent)
Present study	75	Median 18	Median 51.5	93.4%	17%
Liscak et al., 2014	44	Median 20	Median 118	98%	4%
Gandía-González et al., 2014	58	Mean 13.6	Mean 86.4	94.8%	8.6%
Sheehan et al., 2012*	132	Median 15	Median 50.5	93%	15%
Lee et al., 2011	14	Mean 13.7	Median 40.3	100%	7%
Chen et al., 2010	15	Mean 14.6	Mean 43.2	80%	11%
Genç et al., 2010	18	Mean 15.6	Median 41.5	94.4%	5.5%
Miller et al., 2009	5	Mean 15	Mean 34	100%	0%
Ganz & Abdelkarim, 2009	14	Mean 13.6	Mean 28	100%	7%
Sharma et al., 2008	13	Mean 16.3	Median 24	100%	7.7%
Bitaraf et al., 2006	14	Median 18	Median 18.5	100%	0%
Varma et al., 2006	17	Median 15	Median 48	76.4%	11.8%
Feigl & Horstmann, 2006	12	Mean 17	Mean 33	100%	8.3%
Gerosa et al., 2006	20	Mean 17.3	Median 50.9	95%	10%
Sheehan et al., 2005	8	Median 15	Median 32	100%	0%
Pollock, 2004	39	Mean 14.9	Mean 44	98%	15%
Eustacchio et al., 2002	19	Median 14	Median 86.4	94.7%	0%
Foote et al., 2002	25	Median 15	Median 73	100%	0%
Saringer et al., 2001	13	Median 12	Mean 50	100%	15%
Jordan et al., 2000	8	Median 16.3	Mean 27	33%	12.5%
Liscak et al., 1999*	52	Median 16.5	Median 24	100%	5.8%
Eustacchio et al., 1999	10	Median 13.5	Median 37.6	100%	0%
Foote et al., 1997	9	Median 15	Median 17	100%	0%

* Multicenter study.

with the use with the use of linear accelerator and CyberKnife radiosurgery technologies. In a systematic review and meta-analysis of 19 available radiosurgical series including such technologies and comprising 335 patients, Guss et al.³¹ reported a tumor control rate of 97% and a clinical control rate of 95% across all studies.

Lastly, it is worth mentioning that in an earlier comparative study of results between radiosurgery and microsurgical resection,²⁹ 374 patients were treated with surgery; the rate of GTR at the primary surgery was 88.2%, and new postoperative CN deficits occurred in 22%–59% patients, CSF leak in 8.3%, and death in 1.3%. The recurrence rate was 3.1%. Conversely, in 142 patients treated with GKRS, the tumor control rate was 97.8%, clinical improvement was noted in 39%, the morbidity rate was 8.5%, and there were no deaths.

Conclusions

Gamma Knife radiosurgery is a safe and effective primary treatment as well as salvage therapy for residual and recurrent cases of glomus jugulare and tympanicum tumors. It offers a low risk-versus-benefit treatment option with stable long-term tumor control rates and minimal side effects. Treatment at an early stage before tumors attain a large size potentially reduces posttreatment complications. Catecholamine-secreting tumors respond to GKRS with size reduction, although there is a latency period for

hormone level normalization. This series, to the best of our knowledge, constitutes the largest single-center study. It confirms and validates the findings of previously published series.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ibrahim, Yianni, Rowe. Acquisition of data: Ibrahim. Analysis and interpretation of data: Ibrahim, Ammori, Grainger. Drafting the article: Ibrahim, Yianni. Critically revising the article: Ibrahim, Ammori, Yianni, Rowe, Radatz. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ibrahim. Statistical analysis: Ibrahim, Ammori.

Supplemental Information

Previous Presentations

Portions of this work were presented as an oral presentation at the British Radiosurgery Society meeting held in Sheffield, United Kingdom, on May 21, 2013.

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