Comparative Neurologic Outcomes of Salvage and Definitive Gamma Knife Radiosurgery for Glomus Jugulare: A 20-Year Experience

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Abstract

Objective This case series investigates management of glomus jugulare (GJ) tumors utilizing definitive and salvage Gamma Knife stereotactic radiosurgery (GKSRS).

Methods A retrospective chart review was performed to collect data. Statistical analysis included patient, tumor, and treatment information.

Results From 1996 to 2013, 17 patients with GJ received GKSRS. Median age was 64 years (range, 27–76). GKSRS was delivered for definitive treatment in eight (47%) and salvage in nine (53%) patients. Median tumor volume was 9.8 cm³ (range, 2.8–42 cm³). Median dose was 15 Gy (range, 13–18 Gy). Median follow-up was 123 months (range, 38–238 months). Tumor size decreased in 10 (59%), stabilized in 6 (35%), and increased in 1 patient (6%). Overall neurological deficit improved in 53%, stabilized in 41%, and worsened in 6% of patients. Overall cause-specific survival was 100%, and actuarial local control was 94%. Eighty-eight percent of patients without prior resection experienced neurologic deficit improvement, while 25% of patients with prior resection experienced neurologic improvement ($p = 0.02$).

Conclusion Gamma Knife radiosurgery provides effective long-term control of GJ and overall improvement or stabilization of neurological deficit in most patients. Patients with prior resection are less likely to experience improvement of neurologic deficit.

Keywords

- glomus jugulare
- Gamma Knife
- radiosurgery
- salvage

Introduction

Glomus jugulare (GJ) tumors are benign paragangliomas that typically arise from glomus bodies located in the dome of the jugular bulb. These tumors have a low incidence, occurring in 1 in 1.3 million people.¹ GJ tumors are often highly vascularized, locally invasive, and challenging to treat due to

proximity to critical neurovascular structures.^{2–4} Options for treatment include resection alone, resection combined with selective embolization and/or radiation, and radiation alone.^{2–10}

Historically, gross total resection (GTR) has been regarded as the treatment of choice for GJ tumors.^{2–4,11–13} However, GTR is not possible in a significant number of patients, despite

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using combined techniques.^{2,14} Although GJ tumor patients with GTR experience high tumor control (85–95%), they also have higher levels of new or worsened cranial nerves (CNs) IX to XI deficit (between 18 and 40%) compared with stereotactic radiosurgery (SRS), or subtotal resection with external beam radiation therapy (EBRT).^{8,15} These surgical risks have led to the rise of SRS as a treatment option for GJ tumors.^{8,16}

SRS has been shown to have similar tumor control to GTR (95–99%) with reduced morbidity and very low rates secondary malignancy (< 1%).^{6–8,16–19} However, there is a lack of data surrounding long-term outcomes for GJ treated with SRS for primary tumor control and salvage after prior resection. The purpose of this study is to investigate long-term outcomes in patients with GJ tumor treated with primary SRS and SRS for salvage after prior resection using Gamma Knife SRS (GKSRS).

Methods

The University of Tennessee Institutional Review Board approved this retrospective review. The Memphis Gamma Knife Center and Semmes Murphey Neurologic and Spine Institute databases were reviewed to identify patients aged older than 18 years who underwent GKSRS for GJ from 1996 to 2013. GKSRS was performed with the Leksell Gamma Knife. Medical records, radiographic studies, and operative reports were evaluated. Study end points were defined as radiographic tumor control and clinical neurologic deficit persistence.

Patient Population

During the 18-year study period, 17 patients were treated for GJ. All patients receiving GKSRS were evaluated by a multidisciplinary team of neurosurgeons and radiation oncologists prior to treatment. Data collected included age at treatment, sex, race, clinical and radiographic workup, history of prior resection or radiation, tumor histology, tumor site, and GKSRS treatment dosimetry. GKSRS treatment data included maximum dose, isodose line percentage, 50% dose, volume receiving 50% dose, and number of isocenters. If histologic specimens were not obtained, diagnosis was based on clinical exam and radiography using magnetic resonance imaging (MRI) and/or computed tomography scan.

Clinical and Radiologic Outcome Assessment

Acute and late complications, clinical outcome, radiographic tumor control, residual neurologic deficit, and secondary malignancy data were collected in follow-up. Clinical outcome was assessed by patient history and a complete neurologic exam including CN examination. MRI surveillance occurred at 6 months after treatment and at annual intervals beginning 12 months after GKSRS. Tumor volume was determined in cubic centimeters. Patient neurologic and radiographic end points were determined to be improved, stable, or worsened compared with their pretreatment status. Any percentage increase in tumor volume during follow-up compared with tumor volume at the time of GKSRS was categorized as recurrence and treated

with GKSRS. Tumors were categorized as controlled if their volumes remained unchanged or decreased compared with time of GKSRS.

Statistical Analysis

All statistics were calculated using SPSS v.22 (IBM). Symptomatology was matched to CN for analysis. Univariate analysis was performed for prognostic factors related to neurologic deficit improvement. These variables included age, prior resection and radiation, tumor volume, max dose, and number of isocenters. Statistical significance was determined using independent *t*-test and Fisher's exact test. Kaplan–Meier (KM) curves were used to plot progression-free survival, and statistical significance was calculated using the log rank test. Significance was determined as $p < 0.05$.

Results

From 1996 to 2013, GKSRS was used to treat 17 patients with GJ. Median follow-up was 123 months (range, 38–238 months). Median age at GKSRS was 64 years (range, 27–76). Of the 17 patients, 10 were female and 7 were male. Ten (59%) patients were Caucasian, 5 (29%) were African American, and 2 (12%) were Hispanic. One patient had known familial paragangliomas.

Primary treatment with GKSRS was performed in eight (47%) patients. Salvage GKSRS was performed in nine (53%) patients. These patients had previously received resection and active surveillance and were found to have radiographic recurrence. Three patients (18%) had previously received adjuvant EBRT before salvage GKSRS—all of these patients were initially managed in the 1970s to 1980s. One received EBRT prior to resection, and two received adjuvant EBRT to gross residual disease after subtotal surgical resection.

Clinical Presentation

Tumors were left sided in 11 (65%) and right sided in 6 (35%). The most common presenting symptoms were dysphonia and hearing loss, seen in 59 and 65% of patients, respectively. No tumors were tested to prove catecholamine production. A full list of patient clinical characteristics before and after GKSRS is listed in ► **Table 1**.

Management

GKSRS was performed in a single session in all cases. Stereotactic MRI was utilized for treatment planning. Treatment goal was to cover the tumor with a 50% or higher isodose line. Median tumor volume at GKSRS was 9.8 cm³ (range, 2.8–42.0 cm³). A median dose of 15 Gy (range, 13–18 Gy) was delivered to the 50% isodose line. The median number of isocenters was 6 (range, 1–26).

Clinical Outcome

No patients died or experienced secondary malignancy. One (6%) patient with multiple comorbidities (i.e., hypertension, hyperlipidemia, diabetes, dementia prior to GKSRS treatment) experienced cerebellar stroke contralateral to

Table 1 Clinical characteristics of patients before and after GKSRS

Symptom (CN)	Number before GKSRS (%)	Number after GKSRS (%)
Facial numbness (V)	1 (6)	1 (6)
Facial palsy (VII)	3 (18)	1 (6)
Tinnitus (VIII)	8 (47)	3 (18)
Vertigo (VIII)	5 (29)	1 (6)
Hearing loss (VIII)	11 (65)	4 (24)
Dysphagia (IX, X, XII)	7 (41)	5 (29)
Dysphonia (IX, X, XII)	10 (59)	5 (35)
Hoarseness (X)	7 (41)	5 (29)
Accessory paresis (XI)	4 (24)	3 (18)
Tongue fasciculation (XII)	4 (24)	4 (24)

Abbreviations: CN, cranial nerve; GKSRS, Gamma Knife stereotactic radiosurgery.

the side of treatment 5 years after salvage GKSRS at the age of 76 years. Patients previously treated with surgical resection and EBRT did not experience adverse short- or long-term radiation complications.

One (6%) patient treated with salvage GKSRS experienced recurrence 5 years after GKSRS. This patient alone experienced worsening CN deficit, representing with CN VI deficit (i.e., lateral gaze diplopia and headache) due to cavernous sinus invasion of recurrent GJ tumor. This recurrent tumor clinically and radiographically stabilized for 18 months of follow-up after treatment with intensity modulated radiation therapy to a dose of 54 Gy in 30 fractions. All other patients experienced stabilization (41%) or improvement (53%) of presenting neurologic deficits. Overall actuarial local control was 94%, progression-free survival was 94%, and overall cause-specific survival was 100%. ▶**Fig. 1** contains KM curve of progression-free survival (PFS).

Fig. 1 Kaplan Meier analysis of PFS.

Tumor Volume

Tumor size decreased in 10 patients (59%), stabilized in 6 patients (35%), and increased in 1 patient (6%). For tumors that decreased, the mean tumor volume change was 2.0 cm³ (range, 1.5–7.3 cm³) with an overall mean percentage volume change of 46% (range, 20–85%). When tumors that responded were divided into percentile and quartiles for volume change, the results were as follows: 5 (50%) reduced 1 to 25%, 2 (20%) reduced 26 to 50%, 2 (20%) reduced 51 to 75%, and 1 (10%) reduced more than 76%. Although 60% of patients with volume reduction realized that reduction in their tumor within 5 years, 40% of these patients experienced initial volume change after 5 years. The single patient who experienced disease progression progressed 60 months after treatment. One patient with familial paraganglioma was treated with salvage GKSRS has experienced no recurrence 174 months since SRS. ▶**Fig. 2** contains KM analysis of number of patients with tumor volume decrease over time by treatment modality.

Symptomatic Outcome

The most improvement of individual symptoms was seen in patients who experienced dysphonia (50%), pulsatile tinnitus (63%), facial palsy (63%), hearing loss (64%), and vertigo (80%). Less improvement was seen in patients experiencing hoarseness (29%), dysphagia (29%), and accessory paresis (25%). No improvement of symptoms was seen in patients who experienced tongue fasciculation or facial numbness. Patients with improvement in facial palsy experienced partial improvement in their ability to move their forehead and close their eye after GKSRS.

Comparative Outcome by Cranial Nerve

Symptomatology was matched to associated CN for analysis. Overall neurological deficits improved in 53%, stabilized in 41%, and worsened in 6% of patients. No patients presented with CNs I to IV or VI deficits. Overall improvement in individual CN deficit and percentage of patients experiencing improvement was as follows: V (0%), VII (67%), VIII (63–80%), IX/X (combined 29–50%), XI (25%), and XII (0%). Ranges

Fig. 2 Kaplan-Meier analysis of tumor volume decrease.

Fig. 3 (A) Definitive GKSRS CN deficit resolution. (B) Salvage GKSRS CN deficit resolution. CN, cranial nerve; GKSRS, Gamma Knife stereotactic radiosurgery.

represent the resolution of individual symptoms attributed to corresponding CN, as detailed in ►Table 1. Only one patient treated with salvage GKSRS experienced CN deficit worsening, described earlier. A comparison of CN deficit before and after GKSRS by treatment type (definitive vs. salvage) is presented in ►Fig. 3.

Of the patients without prior resection, 7 (89%) experienced neurologic deficit improvement, while 2 (25%) of those with prior resection experienced neurologic improvement ($p = 0.02$). Thus, prior resection was predictive of persistent neurologic deficit in patients treated with GKSRS for GJ. Tumor volume, prior radiation, and GKSRS dosimetry did not correlate to neurologic outcome or tumor control.

Discussion

GJ tumors represent an oncologic challenge. Although local control rates remain high, patients often recur unpredictably.^{10,15,20} Technological advances in the past 50 years have increased the prominence of multimodality, multispecialty treatment.^{3,5,8,10,11,15,21,22} Debate surrounds the best treatment course, and many practitioners find themselves re-evaluating what treatment will yield the ideal results for their patients. Evidence increasingly points toward excellent outcomes with both neurosurgical and radiosurgical techniques—but which is superior?

This series represents a single institution experience at an academic center. It provides evidence highly controlled for variance between patients treated with four neurosurgeons and one radiation oncology group. We demonstrate a 5-year

actuarial local control rate and progression-free survival of 94% and overall cause-specific survival of 100% with definitive and salvage management with GKSRS, indicating the efficacy and safety of this procedure. This is consistent with prior publications of similar size.^{8,16,17,23,24} However, few studies have elucidated the resolution of neurologic deficit by individual CN and tumor volume across time.

What our study reveals is of practical value to patients and their families. Often patients ask “Will I get better?” and “What can I expect?” This series assists to answer such questions. Overall, 75% of patients treated with definitive or salvage GKSRS with CN deficits at presentation experienced improvement in their deficit—up to more than half of patients with pulsatile tinnitus experiencing improvement.

For patients treated with definitive GKSRS, deficits in CNs VIII and X experienced the highest response—25% of CNs VIII and X deficits improved, respectively. Patients with CN XI deficits were much less likely to improve with definitive GKSRS, improving in only 13% of patients. No patients with CN XII treated with definitive GKSRS improved.

For patients treated with salvage GKSRS, outcomes are slightly less encouraging. Only one-third of patients treated with salvage GKSRS experienced improvement in their deficit. At best, 22% of CN VII deficits improved after salvage GKSRS. Eleven percent of patients with CNs VIII, X, and XII deficits improved, respectfully. No patients with CNs V and XI deficits improved. Although salvage GKSRS provided excellent local control, neurologic deficit was statistically less likely to resolve in overall comparison to definitive GKSRS ($p = 0.02$).

Notably, GJ tumor size decreased minimally with therapy. Only 25% of patients realized tumor volume change more than 50%. Response in our cohort persisted over time—treatment response was seen up to 5 years from GKSRS in 40% of patients whose tumor volume decreased. The single patient who recurred after salvage GKSRS did so 5 years after therapy, re-emphasizing the need for long-term surveillance of these biologically unpredictable tumors.

With its equivalent local control rate and overall survival, a superior result in CN deficit resolution, and overall decreased surgical complication risk, our institution has moved toward primary management of GJ tumors with GKSRS. However, for tumors with symptomatic brain stem compression, surgical resection remains the preferred primary treatment modality because there is minimal change in tumor size after treatment with GKSRS. Our reason explaining this approach is confirmed in our results.

Although useful to both practitioners and patients, this study has limitations. GJ tumors are rare, and like other studies, our population is of limited size. Neurologic deficits reported in this study (see ►Table 1) are patient-reported outcomes and are dependent on subjective experience, with the exception of tongue fasciculation, accessory paresis, and facial nerve palsy. It is possible that this subjective evaluation could reflect a patient's adaptation to their deficit over time. Our 5-year actuarial control should be interpreted with caution for this type of tumor—other studies have reported recurrence up to 7 years from treatment.²⁵

Variance exists between patient selections—due to the lack of evidence for definitive GKSRS in the late 1990s, patients treated early in our series were more likely to be management with GKSRS for salvage. No patients in this group have died, and only one experienced recurrence. This study re-enforces the long-term safety of GKSRS. For patients treated with salvage GKSRS, CN deficit and tumor volume prior to initial surgery and residual tumor volume and deficit after that surgery are not reported. An analysis of neurologic deficit—including these findings comparing patients with GJ tumors treated with definitive resection, definitive GKSRS, and salvage GKSRS—will be published in the future article.

Evidence surrounding appropriate selection for resection is lacking, and future studies may elucidate systematic approaches to predict which patients could be best managed with resection alone or resection combined with RT.^{4,26} Randomized controlled trials comparing management of GJ tumors with primary resection versus GKSRS versus combined modality have not been published to guide treatment for patients with this disease; however, due to the low incidence of this tumor, these are unlikely. Future prospective registries for GJ tumors could be utilized to overcome this limitation.

Conclusion

Gamma Knife radiosurgery provides effective long-term control of GJ and overall improvement or stabilization of neurological deficit in most patients. Patients with prior resection are less likely to experience improvement of neurologic deficit.

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References

- Moffat DA, Hardy DG. Surgical management of large glomus jugulare tumours: infra- and trans-temporal approach. *J Laryngol Otol* 1989;103(12):1167–1180
- Al-Mefty O, Teixeira A. Complex tumors of the glomus jugulare: criteria, treatment, and outcome. *J Neurosurg* 2002;97(6):1356–1366
- Michael LM II, Robertson JH. Glomus jugulare tumors: historical overview of the management of this disease. *Neurosurg Focus* 2004;17(2):E1
- Tomasello F, Conti A. Judicious management of jugular foramen tumors. *World Neurosurg* 2015;83(5):756–757
- Arthur K. Radiotherapy in chemodectoma of the glomus jugulare. *Clin Radiol* 1977;28(4):415–417
- Foote RL, Coffey RJ, Gorman DA, et al. Stereotactic radiosurgery for glomus jugulare tumors: a preliminary report. *Int J Radiat Oncol Biol Phys* 1997;38(3):491–495
- Gottfried ON, Liu JK, Couldwell WT. Comparison of radiosurgery and conventional surgery for the treatment of glomus jugulare tumors. *Neurosurg Focus* 2004;17(2):E4
- Ivan ME, Sughrue ME, Clark AJ, et al. A meta-analysis of tumor control rates and treatment-related morbidity for patients with glomus jugulare tumors. *J Neurosurg* 2011;114(5):1299–1305
- Larouere MJ, Zappia JJ, Wilner HI, Graham MD, Lundy LB. Selective embolization of glomus jugulare tumors. *Skull Base Surg* 1994;4(1):21–25
- Suárez C, Rodrigo JP, Bödeker CC, et al. Jugular and vagal paragangliomas: Systematic study of management with surgery and radiotherapy. *Head Neck* 2013;35(8):1195–1204
- McCabe BF, Fletcher M. Selection of therapy of glomus jugulare tumors. *Arch Otolaryngol* 1969;89(1):156–159
- Pareschi R, Righini S, Destito D, Raucci AF, Colombo S. Surgery of Glomus Jugulare Tumors. *Skull Base* 2003;13(3):149–157
- Ramina R, Maniglia JJ, Fernandes YB, Paschoal JR, Pfeilsticker LN, Coelho Neto M. Tumors of the jugular foramen: diagnosis and management. *Neurosurgery* 2005;57(1, Suppl):59–68, discussion 59–68
- Patel SJ, Sekhar LN, Cass SP, Hirsch BE. Combined approaches for resection of extensive glomus jugulare tumors. A review of 12 cases. *J Neurosurg* 1994;80(6):1026–1038
- Lope Ahmad RA, Sivalingam S, Konishi M, De Donato G, Sanna M. Oncologic outcome in surgical management of jugular paraganglioma and factors influencing outcomes. *Head Neck* 2013;35(4):527–534
- Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2011;81(4):e497–e502
- Gilbo P, Morris CG, Amdur RJ, et al. Radiotherapy for benign head and neck paragangliomas: a 45-year experience. *Cancer* 2014;120(23):3738–3743
- El Majdoub F, Hunsche S, Igressa A, Kocher M, Sturm V, Maarouf M. Stereotactic LINAC-radiosurgery for glomus jugulare tumors: a long-term follow-up of 27 patients. *PLoS One* 2015;10(6):e0129057
- Gandía-González ML, Kusak ME, Moreno NM, Sárraga JG, Rey G, Álvarez RM. Jugulotympanic paragangliomas treated with Gamma Knife radiosurgery: a single-center review of 58 cases. *J Neurosurg* 2014;121(5):1158–1165
- Carlson ML, Sweeney AD, Wanna GB, Netterville JL, Haynes DS. Natural history of glomus jugulare: a review of 16 tumors managed with primary observation. *Otolaryngol Head Neck Surg* 2015;152(1):98–105
- Wang ML, Hussey DH, Doornbos JF, Vigliotti AP, Wen BC. Chemodectoma of the temporal bone: a comparison of surgical and radiotherapeutic results. *Int J Radiat Oncol Biol Phys* 1988;14(4):643–648
- Moore GR, Robbins JP, Seale DL, Fitz-Hugh GS, Constable WC. Chemodectomas of the middle ear. A comparison of therapeutic modalities. *Arch Otolaryngol* 1973;98(5):330–335
- Wong BJ, Roos DE, Borg MF. Glomus jugulare tumours: a 15 year radiotherapy experience in South Australia. *J Clin Neurosci* 2014;21(3):456–461
- Liscak R, Urgosik D, Chytka T, et al. Leksell Gamma Knife radiosurgery of the jugulotympanic glomus tumor: long-term results. *J Neurosurg* 2014;121(Suppl):198–202
- Schuster D, Sweeney AD, Stavas MJ, et al. Initial radiographic tumor control is similar following single or multi-fractionated stereotactic radiosurgery for jugular paragangliomas. *Am J Otolaryngol* 2016;37(3):255–258
- Sager O, Dincoglan F, Beyzadeoglu M. Stereotactic radiosurgery of glomus jugulare tumors: current concepts, recent advances and future perspectives. *CNS Oncol* 2015;4(2):105–114