Safety and Efficacy of Primary Multisession Dose Fractionated Gamma Knife Radiosurgery for Jugular Paragangliomas

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■ BACKGROUND: **While multisession dose fractionated Gamma Knife radiosurgery (DFGKS) is common, its use has never been described for jugular paragangliomas (JP), which are notoriously difficult to treat.**

■ OBJECTIVE: **To define efficacy, safety, and complication profile of DFGKS in 2 or 3 consecutive sessions for the treatment of a cohort of 10 cases of JP.**

■ METHODS: **Between 2012 and 2017, 10 patients with JP were treated with DFGKS in 2 or 3 sessions, because it was not safe to treat the lesion in a single session because of the large volume or proximity to organs at risk. The small to medium-sized JP are treated with 16–22 Gy radiation, but the large-volume JP were treated with 23–25 Gy radiation dose. The Leksell G frame was kept in situ during the whole procedure. The tumor volumes on pretreatment and posttreatment imaging were compared, using the Leksell Gamma Plan treatment plan software to assess tumor progression. The patients were regularly evaluated for their clinical outcome with radiologic correlation.**

■ RESULTS: **The mean radiologic follow-up was 39 months (range, 12–78 months). The mean marginal dose for 3 fractions and 2 fractions was 7.64 Gy at 50% and 11.2 Gy at 50%, respectively. The mean tumor size was 29.9 cm^3 (range, 9.95–47.63 cm^3) at treatment and 21.9 cm^3 (range, 8.83–37.5 cm^3) at follow-up (suggestive of 26.7% reduction). Tumor control was achieved in all patients (100%). Of 110 potential neurologic problems (signs/symptoms) evaluated (11 in each patient), 56 (50.9%) were present preoperatively. Of them, 27 (48.2%) improved and 29 (51.8%) stabilized after treatment. There were 2 new-onset neurologic problems (of 110, 1.8%) attributable to treatment (new-onset headache and spinal accessory paresis). No patient had any permanent neurologic deterioration.**

■ CONCLUSIONS: **DFGKS for large-volume JP leads to acceptable progression-free survival, tumor control rate, and symptomatic improvement. It may be preferred to surgery or fractionated radiotherapy given its better safety, efficacy, and complication profile.**

INTRODUCTION

Background/Rationale

The surgical management of jugular paraganglioma (JP) is often met with pessimistic outcomes in terms of both tumor control and morbidity profile because of topographic anatomy and tumor vascularity. The different modalities of management are microsurgical resection,

Key words
- Cranial neuropathy
- Dose fractionated Gamma Knife radiosurgery
- Jugular paraganglioma
- Linear quadratic model
- Radiosurgery

Abbreviations and Acronyms
AVM: Arteriovenous malformation
CN: Cranial nerve
DFGKS: Dose fractionated Gamma Knife radiosurgery
GKS: Gamma Knife radiosurgery
GTV: Gross tumor volume
IMRT: Intensity modulated radiotherapy
JP: Jugular paraganglioma
LQ: Linear quadrantic
MRI: Magnetic resonance imaging
RRC: Radiosurgery Response Classification
SRS: Stereotactic radiosurgery

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conventional radiotherapy, intensity modulated radiotherapy (IMRT), and stereotactic radiosurgery (SRS). Numerous studies have already established primary Gamma Knife radiosurgery (GKS) as a preferred treatment modality for most such patients, with tumor control rates equivalent to or better than surgery, with the lowest chances of collateral damage. With a large tumor, radiation spillage to organs at risk and cochlear preservation can be limiting factors for conventional primary single-session GKS. Dose fractionated GKS (DFGKS) is a suitable alternative to push the limitations of radiosurgery in such clinical dilemmas. There is a lack of robust literature on DFGKS because of earlier skepticism, perceived discomfort of the frame for a longer duration, and ill-defined radiobiology of such rare tumors.

METHODS

Study Design

A prospective cohort study was carried out.

Participants and Setting

With the approval of the institutional ethics committee, we offer DFGKS as a primary treatment modality for patients with large volume JP (>10 cm^3) as an alternative to single-session GKS, IMRT, or primary surgery. Primary single-session GKS was not feasible in these patients because of unacceptable radiation toxicity to the brainstem or functional cochlea or the large volume of the tumor. Patients with clinically significant brainstem compression were excluded from this treatment and were offered surgical resection as the primary treatment. With informed consent, 14 patients received DFGKS at our institute for a glomus jugulare tumor from January 2012 to December 2017. Patients with previous surgery, angioembolization, radiotherapy, and those with less than 12 months follow-up were excluded. Ten patients were included in the retrospective analysis of a prospectively maintained database on clinicoradiologic parameters with comparative evaluation in a protocol-based manner.

Variables

We established the diagnosis based on the patient's history and clinicoradiologic examination.[1] All patients underwent magnetic resonance imaging (MRI) of the brain, and close differentials were ruled out on expert radiologic opinion. In a few patients, the computed tomography head scan was performed to know the extent of bone destruction and digital subtraction angiography for the vascular pattern. In all cases, GKS was performed as the first and primary treatment basis. Clinical, otologic, audiometry, hormonal, and neuropsychological assessment was performed at baseline, 6 months, and then yearly for the first 3 years, and after that, every 2 years or when clinically indicated. Whenever required, the patient underwent follow-up examination.

Tumor Volume Delineation. The initial tumor volume was determined by contouring the tumor from the imaging performed on the day of DFGKS using the Leksell Gamma Plan software (Elekta Instruments, Atlanta, Georgia, USA).

Radiosurgical Treatment. The protocol of stereotactic frame placement and image acquisition using MRI was described in our earlier report.[1,2] On the first day of the procedure, the Leksell G frame was fixed on the patient's head under local anesthesia. For large-volume tumors with significant extracranial extension, the frame should be fixed as low as possible to safely irradiate the tumor and avoid the collision error. The patients were treated in 3 sessions on a daily basis, or 2 sessions on an alternate day basis, in the same hospital admission with the frame in situ, firmly fixed to their head throughout the treatment. All attempts were made to start the next day's schedule as close as possible to that of the previous day, attempting a gap of 22–24 hours between the start of the 2 schedules. The patient was instructed that the frame should not be loosened during the treatment. For image acquisition, one should be sure to reach the lower margin of the tumor, which frequently extends along the lower cranial nerves. The gross tumor volume (GTV) was represented by the lesion delineated on MRI. The entire GTV was covered with 50% isodose line (prescription isodose). All radiosurgical treatments were performed using Leksell Gamma Knife Perflexion machine (Elekta Instruments, Norcross, Georgia, USA).

The small to medium-sized JP are treated with 16–22 Gy at 50% isodose radiation, but the large-volume JP were treated with 23–25 Gy at 50% isodose. DFGKS was delivered in 2 or 3 fractions according to the volume of the JP (>10 cm^3) or proximity to the brainstem/cochlea. This approach facilitated enough time for recovery of healthy tissue and maintained the efficacy of treatment of the target tumor. The details of DFGKS marginal dose calculation for using biological effective dose according to the linear quadratic (LQ) model have been previously reported by our team[1,2] (**Table 1**). All patients were treated with GTV coverage of >97%. Irrespective of the dosing schedule, the cumulative volume of the brain exposed to a daily 8 Gy (adding in all the fractionations) was limited to ≤200 cm^3. With the DFGKS, we aimed to keep 12 Gy volume of the surrounding brain <8 cm^3, 12 Gy volume of brainstem 0.00 cm^3, and 3 Gy volume of the cochlea <5% per fraction, because there is a theoretic risk of accumulated radiation toxicity in hypofractionation regimens. A 3-day fractionation scheme was chosen only if the organs at risk were receiving more than accepted radiation in a 2-day scheme. The cumulative radiation exposure to the cochlea and brainstem in all fractions was calculated, and the plans were modified to maintain a safety margin. Oral dexamethasone was also continued after the procedure for 1 week. Patients were discharged after a day of observation after completion of the procedure.

Follow-Up. The first follow-up imaging (using the same MRI sequences obtained during DFGKS) was performed at 3 months, then at 6 months, and once a year or 2 years after that. The clinical and radiologic outcomes of all patients were evaluated up to the last available follow-up. The tumor volumes on pretreatment and posttreatment imaging were compared, using the Leksell Gamma Plan treatment plan software to assess tumor progression. We used Radiosurgery Response Classification (RRC) described by Feiglet al.[3] to describe the radiologic response of tumor. Shrinkage of tumor >10% is RCC grade I. Treatment response with unchanged tumor volume is RRC grade 2. RRC grade 3 is defined as treatment nonresponse with tumor growth after SRS.

Table 1. Dose per Fraction Applicable to Normal Tissue ($\alpha/\beta = 3$ Gy) and Tumor ($\alpha/\beta = 3$ Gy) in Dose Fractionated Gamma Knife Radiosurgery Scheme

Single-Fraction Dose (Gy)	Dose per Fraction of 2-Fraction Schedule		Dose per Fraction of 3-Fraction Schedule	
$\alpha/\beta = 3$ Gy Transition Dose = 6 Gy	25% Dose Deduction (Total Treatment Dose)	15% Dose Deduction (Total Treatment Dose)	25% Dose Deduction (Total Treatment Dose)	15% Dose Deduction (Total Treatment Dose)
4	2.53 (5.06)	2.53 (5.06)	1.90 (5.70)	1.90 (5.70)
5	3.22 (6.44)	3.22 (6.44)	2.45 (7.35)	2.45 (7.35)
6	3.91 (7.82)	3.91 (7.82)	3.00 (9.00)	3.00 (9.00)
7	4.40 (8.80)	4.50 (9.00)	3.40 (10.20)	3.45 (10.35)
8	4.83 (9.66)	5.02 (10.04)	3.74 (11.22)	3.89 (11.67)
9	5.20 (10.40)	5.51 (11.02)	4.05 (12.15)	4.31 (12.93)
10	5.53 (10.96)	6.00 (12.50)	4.31 (12.78)	4.68 (14.64)
11	5.80 (11.60)	6.45 (12.90)	4.51 (13.53)	5.05 (15.15)
12	6.00 (12.00)	6.84 (13.68)	4.68 (14.04)	5.37 (16.11)
13	6.53 (13.06)	7.44 (14.88)	5.11 (15.33)	5.85 (17.55)
14	7.05 (14.10)	8.03 (16.06)	5.54 (16.62)	6.33 (18.99)
15	7.58 (15.16)	8.63 (17.26)	5.96 (17.88)	6.82 (20.46)
16	8.10 (16.20)	9.23 (18.46)	6.39 (19.17)	7.30 (21.90)
17	8.63 (17.26)	9.83 (19.66)	6.82 (20.46)	7.79 (23.37)
18	9.16 (18.32)	10.43 (20.86)	7.25 (21.75)	8.28 (24.84)
20	10.22 (20.44)	11.62 (23.24)	8.10 (24.30)	9.25 (27.75)
21	10.74 (21.48)	12.22 (24.44)	8.53 (25.59)	9.74 (29.22)
22	11.27 (22.54)	12.82 (25.64)	8.96 (26.88)	10.23 (30.69)
23	11.80 (23.60)	13.42 (26.84)	9.39 (28.17)	10.71 (32.13)
24	12.33 (24.66)	14.02 (28.04)	9.82 (29.46)	11.20 (33.60)
25	12.86 (25.72)	14.62 (29.24)	10.26 (30.78)	11.69 (35.07)

Detailed neurologic examination with an emphasis on cranial nerve function was performed at each follow-up. The patient's neurologic status before treatment was used as a reference point, and outcomes were expressed in terms of change from this baseline as improved, unchanged, or worse. Patients with neurologic worsening were evaluated if the worsening was a side effect of radiation or tumor progression. Every adverse event was evaluated as per the criteria given by the Common Terminology Criteria for Adverse Events.[3,4]

Statistical Methods. Descriptive statistics were used to characterize demographic and clinical data. Baseline and posttreatment scores were analyzed by a paired t test and Wilcoxon signed-rank test. Statistical significance was set at $P \leq 0.05$. Data are presented as mean and range for continuous variables and as frequency and percentage for categorical variables. All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, New York, USA).

RESULTS

Participants

Descriptive Data. The patient population consisted of 8 females and 2 males with a mean age of 41.5 years (range, 22–60 years). No patient underwent any previous surgical intervention. The most common symptom at presentation was a headache (80%). The mean tumor volume at presentation was 29.9 cm^3 (range, 9.95–47.63 cm^3). Of patients, 70% had a mixed hearing loss of variable extent at the time of GKS. Patients' characteristics and demographics are summarized in Table 2.

Outcome Data. Seven patients underwent DFGKS in 3 fractions and 3 in 2 fractions. The mean marginal prescription dose at 50% was 7.6 Gy (in 3 fractions) and 11.2 Gy (in 2 fractions). The mean duration of clinical and radiologic follow-up was 39 months (range, 12–78 months). The mean tumor volume at last follow-up was 21.9 cm^3 (range, 8.83–37.5 cm^3). Overall, a 26.7% reduction in mean tumor volume was noted ($P = 0.019$) (Figure 1). Nine of 10 patients (90%) had a >10% reduction in tumor volume (RRC

Table 2. Summary of Baseline Features of 10 Patients of Jugular Paraganglioma who Received Dose Fractionated Gamma Knife Radiosurgery

Patient	Age/Sex	Symptoms and Signs	Marginal Dose (Gy) at 50% Isodose Line × Number of Fractions	Follow-Up (months)	Tumor Volume at Dose Fractionated Gamma Knife Radiosurgery (cm^3)	Tumor Volume at Last Follow-Up (cm^3)
1	36/F	Dysphonia Nasal regurgitation CN 9–12	9 × 3	78	9.95	8.83
2	60/F	Headache Tinnitus Hearing loss	8.1 × 3	76	20.13	14.37
3	58/M	Headache Hearing loss Dysphagia Dysphonia Nasal regurgitation CN 5 and 7–12, Ataxia Limb spasticity	7 × 3	52	34.44	33.94
4	22/F	Ear bleed Headache Tinnitus Hearing loss Dysphagia Dysphonia Nasal regurgitation CN 9, 10, 12	8 × 3	39	28.19	24.24
5	32/M	Ear bleed Headache Tinnitus Hearing loss Dysphonia Diplopia CN 6, 8, 11, 12	7 × 3	42	47.63	19.77
6	32/F	Headache Dysphagia Dysphonia Nasal regurgitation CN 9, 10, 12	7.2 × 3	36	39.72	26.19
7	30/F	Headache Tinnitus Hearing loss Vertigo CN 7, 8	10.6 × 2	20	27.31	22.17
8	58/F	Headache Tinnitus Hearing loss Facial weakness CN 7–10 and 12	7.2 × 3	17	38.53	34.37
9	28/F	Headache Tinnitus Dysphagia Dysphonia Nasal regurgitation Vertigo CN 9, 10, 12	11.3 × 2	18	22.61	14.82

CN, cranial nerve. F, female; M, male.

Continues

Table 2. Continued

Patient	Age/Sex	Symptoms and Signs	Marginal Dose (Gy) at 50% Isodose Line × Number of Fractions	Follow-Up (months)	Tumor Volume at Dose Fractionated Gamma Knife Radiosurgery (cm^3)	Tumor Volume at Last Follow-Up (cm^3)
10	29/F	Ear bleed Tinnitus Hearing loss Dysphagia Dysphonia Vertigo Diplopia CN 6 and 8–12	12 × 2	12	30.45	20.78

CN, cranial nerve. F, female; M, male.

grade I). In patients with >36 months follow-up (n = 6), a 29.3% reduction was present, whereas in patients with <3 years follow-up (n = 4), mean volumetric reduction was 22% (Figures 2 and 3). No patient experienced tumor progression.

The greatest improvement was noticed in the symptoms of headache (100%) and pulsatile tinnitus and started within 3 months of GKS. At follow-up, only 1 patient developed transient new-onset headache, which subsided with a short course of analgesics. Four of 10 patients also had pre-GKS otorrhea, which improved without any other treatment by the end of the first year. Of patients, 20% reported improvement in hearing, and 50% reported having a better voice (Table 3).

Complications. No serious side effects occurred after DFGKS, except for 1 patient who experienced new-onset deficit of the spinal accessory nerve in the form of drooping of the shoulder. No patient gained any improvement in hypoglossal nerve paresis. No patient reported any disabling pain, worsening of vertigo, imbalance, vocal cord paralysis, or local alopecia.[5]

DISCUSSION

JP are rare benign tumors of the chemoreceptor system arising from paraganglia on the superior surface of the jugular bulb within the jugular foramen, with an overall incidence of 0.07–8.6 cases per 100,000 patients.[6-8] JP is reportedly 2–5 times more common in females than males (similar to our study).[7,9,10] JP is located at traditionally remote areas of the skull base surrounded by critical neurovascular structures such as the jugular bulb, the petrous and lacerum parts of the internal carotid artery, lower cranial nerves, brainstem, and inner ear organs. Patients who underwent surgical intervention were more likely to experience functional impairment.[6,11-13] Primary GKS provides the lowest long-term tumor progression and cranial neuropathy compared with gross total resection, subtotal resection, or subtotal resection followed by radiosurgery.[11] Hence, radiosurgery is considered a primary treatment modality for most cases.[14] Many centers worldwide still prefer conventional radiotherapy for large-volume JP or JP with significant extracranial extension for 2 main reasons: 1) radiation injury to the surrounding organs at risk and 2) questionable immobility of the extracranial part of the tumor extending beyond the axis vertebrae. With anecdotal case reports and recently after the introduction of the frameless Gamma Knife machine (i.e., ICON), we have evidence of short-term safety and efficacy for various intracranial diseases.

Proper patient evaluation is of paramount importance in deciding DFGKS as the treatment option.[1,15] Caution is needed in the diagnosis of the disease in the absence of any histopathologic proof. JP is considered a radiologic diagnosis, but there are close differentials (e.g., lower cranial nerve schwannomas, skull base meningiomas, extraskeletal mesenchymal chondrosarcoma, and malignant paragangliomas) (Table 3). In cases of disputed identity, it is always advisable to seek histopathologic evidence. Patients with features of brainstem compression and a high level of catecholamines should be offered cytoreductive surgery as the first treatment option. Every attempt should be made at maximum safe resection (especially for lower cranial nerves) followed by adjuvant radiosurgery for the best outcome.

The Fractionation Scheme for JP

The prescribed marginal dose for JP has been reported to range from 12 to 22 Gy at 50% isodose in various case series. A few fractionated radiation regimes have been prescribed at 45–54 Gy in different fractionation schemes.[16] As in GKS for arteriovenous malformations (AVMs), in which the obliteration rate is higher with increased minimum margin average dose, the aim in glomus tumors, which have their origin in smooth muscle cells and are known to be notoriously hypervascular, is a higher marginal dose without compromising on the safety of the adjacent structures. The most significant argument against single-session GKS for large-volume JP is the volume of the normal brain and organs at risk receiving radiation with the GKS. Ideally, the volume of normal brain parenchyma receiving 12 Gy radiation should not exceed 10 cm^3. The radiation tolerance of brainstem and cochlea in a single-fraction GKS is 12 Gy and 4 Gy, respectively. However, it sometimes becomes impossible to keep the treatment dosages within this range in giant JP.[2] A fractionation scheme (either dose or volume) helps in this aim by minimizing radiation spillage to the surrounding area and

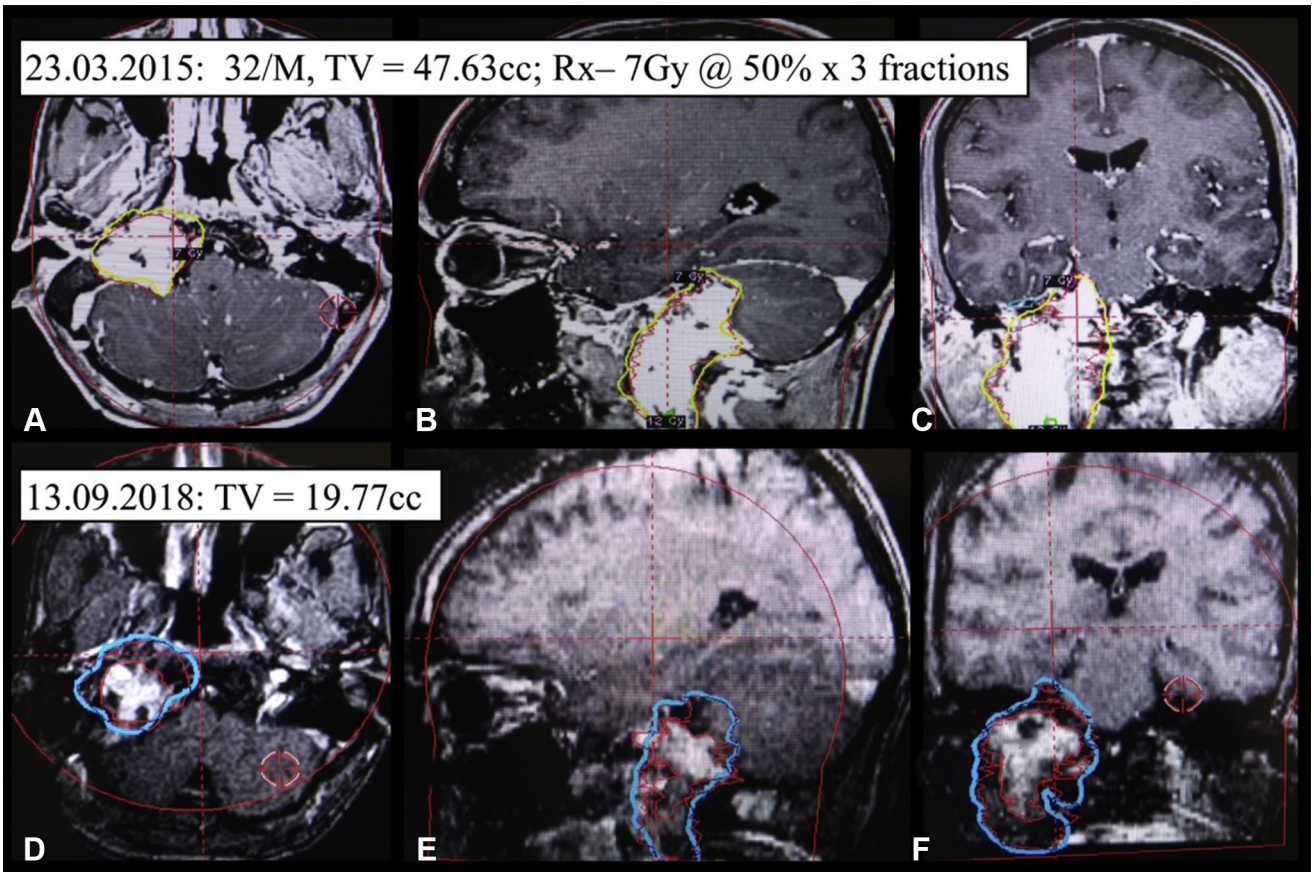

Figure 1. (**A**) Axial, (**B**) sagittal, and (**C**) coronal contrast-enhanced T1-weighted magnetic resonance images of a large right jugular paraganglioma of 47.63 cm^3 volume treated with dose fractionated Gamma Knife radiosurgery with prescription isodose of 7 Gy at 50% in 3 fractions (patient 5, Table 1). Corresponding images (**D**–**F**) of the tumor after 3 years follow-up show a marked reduction in size (tumor volume 19.77 cm^3) and vascularity of tumor.

keeping an interfraction interval helps normal tissue to recover from any radiation injury incurred.[17] Decreasing the time between fractions and the total length of the treatment course should decrease tumor cell repopulation, further enhancing the efficacy of the regimen. The 5 Gy in 5 fraction scheme was not preferred in our setup because it becomes more uncomfortable for the patient with the frame in situ and radiation spillage was maintained in the normal safety limit with our hypofractionation regimen.

Key Results

Our study reported 10 patients with JP treated with DFGKS. To the best of our knowledge, it is the only series on JP reported so far. DFGKS is a recent concept, which gained impetus with the introduction of the frameless model of GKS (the ICON model). The dose calculation for fractionation in IMRT and conventional radiotherapy has traditionally been based on the LQ model. Because of the inherent limitations of the LQ model and high chances of error beyond the dose of 10 Gy per fraction, the same cannot be applied to GKS in principle.[2,15,18,19] Hence, data assessing DFGKS efficacy and complication rates are still lacking and nonstandardized. At present, there are no set standardized guidelines of radiation tolerance of cochlea or brainstem in the fractionated radiosurgery regimen and the literature is still evolving. We have previously reported our experience with large-volume AVMs treated with DFGKS. There have been reports of the treatment of perioptic tumors, AVMs, and pituitary adenomas.[2,14,18,19]

Generalizability. The literature evidence for the ideal management for JP is mostly based on small-volume retrospective studies. Numerous single-institution studies and systematic reviews have established the superiority of primary radiosurgery (both linear accelerator-based and Gamma Knife based) over surgical excision (Table 4). In very large JP with significant intracranial extension, conventional single-session GKS may not be feasible because of

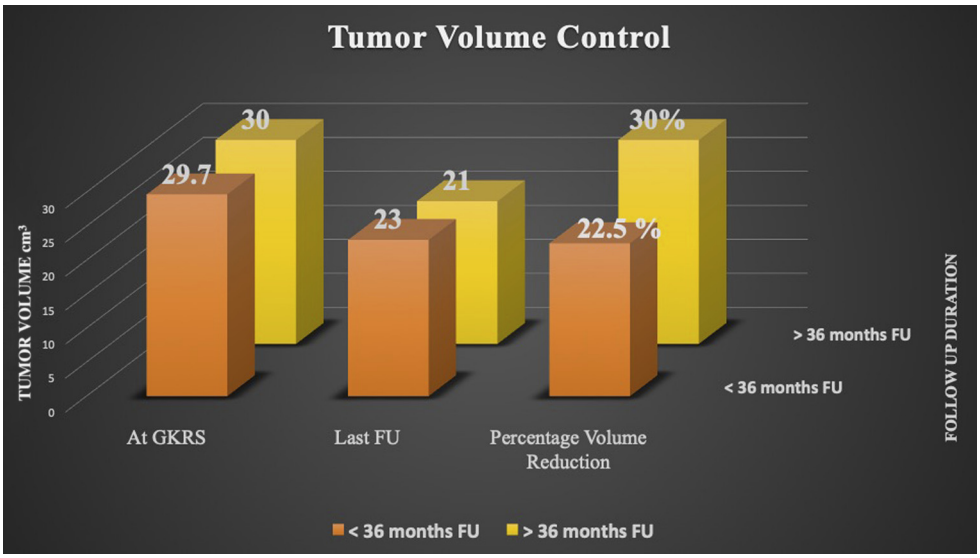

Figure 2. Comparative radiologic response of jugular paraganglioma in patients with short-term (<36 months) and long-term (>36 months) follow-up period. FU, follow-up; GKRS, Gamma Knife radiosurgery.

unacceptable radiation spillage to the brainstem. SRS may also be limited by the need for cochlear preservation in patients with functional hearing. In such situations, surgical excision or linear accelerator SRS/GKS with doses of 5 Gy in 5 fractions is the usual alternative. External beam radiotherapy provides long-term tumor control in the range of 85%–100% with complication rates of 0%-10% (necrosis of temporal bone or brain, mastoiditis, and other local tissue injury). Various radiosurgical series have reported a good outcome with a 12-Gy to 15-Gy marginal dose in single-session GKS.[15] In our personal unpublished experience, a higher dose range of 22–25 Gy provides better tumor control, with rapid improvement of neurologic status (Table 1). The comparative evaluation shows minimal complication profile with GKS compared with external beam radiation therapy.[13] In cases in which the large size or proximity to critical structures limitsthe therapeutic index of single-fraction radiosurgery, hypofractionated stereoradiosurgery has emerged as a viable alternative. Zhong et al.[19] in their review of the literature of hypofractionated stereoradiosurgery for brain metastasis, benign tumors, and AVMs showed comparable efficacy and minimized toxicity. Given that the α/β ratio for tumors is generally higher than that of normal critical structures, the effect of radiation on tumors is relatively less affected by fractionation than is normal brain tissue. We have calculated the fractionated dose for JP keeping α/β ratio at 3. Thus, hypofractionation preferentially spares normal critical structures and maintains its therapeutic effect on tumor cells.[19,26,28,29,32,33,35]

Overall Tumor Control. Tumor control rate in our patients was 100% at a mean follow-up of 39 months (range, 12–78 months). This result is comparable to the single-session GKS series, in which the local tumor control rate was reported in the long-term as 94%–100% (Table 4). Long-term studies have reported a further reduction of the tumor volume even 3 years after GKS. Similar to the study by Pollock,[12] we did not find any correlation between volumetric tumor reduction and the prescribed marginal dose. However, the tumors receiving a marginal dose of ≤12 Gy remain at high risk of treatment failure.[12] We report management of large-volume JP with mean tumor volume 29.9 cm^3 compared with the literature evidence of tumor volume 3.9–9.6 cm^3 (Table 4). Another important consideration that helps in radiosurgical management of large-volume JP is the extracranial extension of the tumor. GKS can easily target lesions extending up to the C2 cervical vertebra because of its better reach and favorable safety profile.[15,36,37]

Improvement in Headache and Tinnitus. The striking improvement in the complaints of headache and tinnitus is noteworthy.[15] All patients reported an improvement in headache (Table 3). The headache in cases of JP might be a dural stretch or vascular headache or both. The pathophysiology behind this improvement is not known. We hypothesize that radiosurgery dampens the vascular flow inside the tumor, with gradual obliteration of the channels that relieve the vascular headache and the pulsatile tinnitus.

Improvement in Cranial Neuropathy. Regarding surgery and radiotherapy treatment, the symptomatic improvement with GKS is noteworthy. Even a subtle volumetric reduction leads to a clinically significant improvement in the signs and symptoms akin to mechanical decompression of the lower cranial nerves. Sheehan et al.[15] reported improvement of cranial neuropathy in 11% of the patients; however, in our experience, 51.8% of patients reported improvement whereas 48.2% reported static

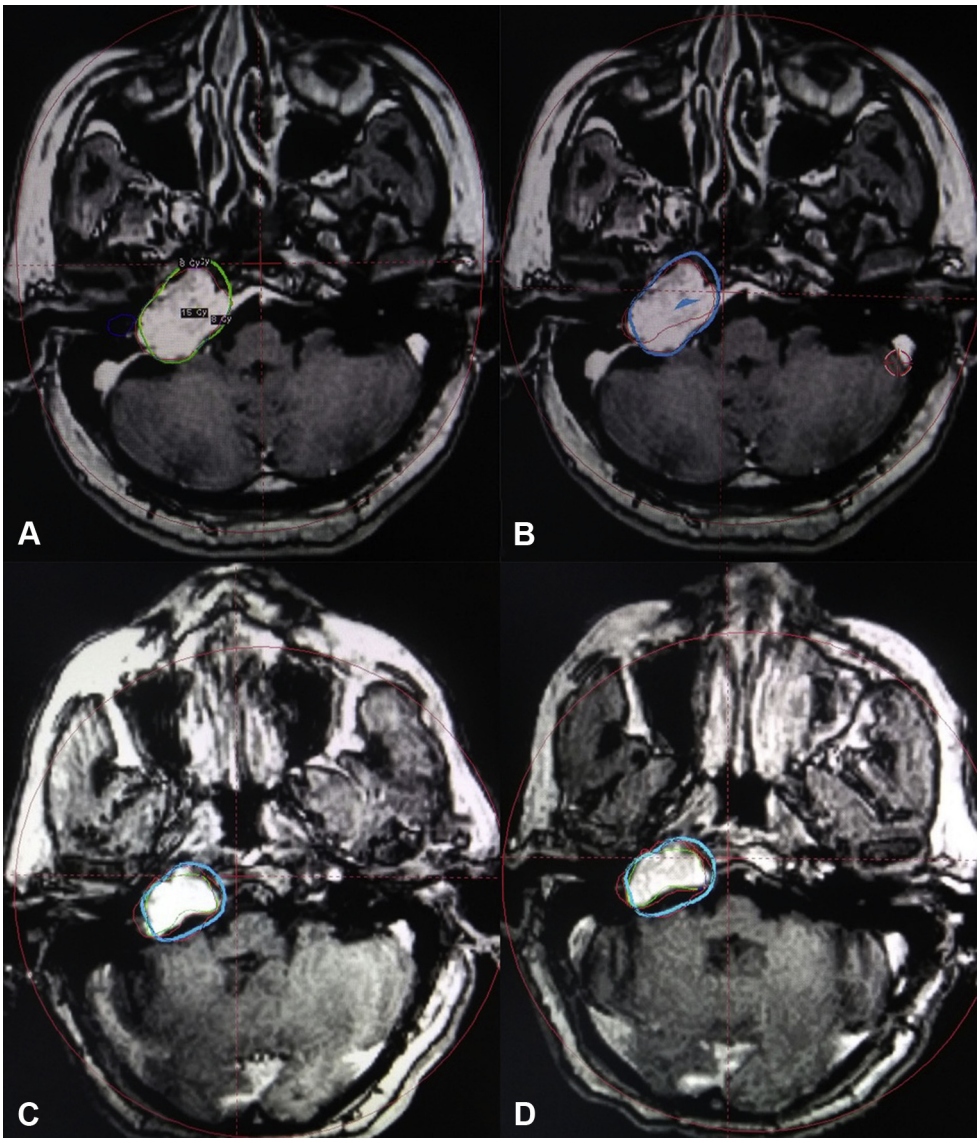

Figure 3. Radiologic response of dose fractionated Gamma Knife radiosurgery in patient 2 (Table 1). Serial gadolinium-enhanced axial T1-weighted images showing jugular paraganglioma at presentation (**A**), at 6 months follow-up (**B**), at 4 years follow-up (**C**) and at 6 years follow-up (**D**). The tumor volumes calculated at these time periods were 20.13 cm^3, 19.88 cm^3, 17.52 cm^3, and 14.37 cm^3, respectively.

neurologic status at short-term follow-up. Lower cranial nerves are sensitive to mechanical stretch and earlier surgical series have reported poor long-term outcome with the frequent onset of new neurologic deficits despite improvement in intraoperative armamentarium and neuromonitoring tools.[11,13] The most common reported complication of single-session GKS is hearing loss, which can be saved in some patients with DFGKS.[12,13] Hearing preservation is better achieved with the fractionation schemes preventing radiation spillage to the basal turn of the cochlea. However, the hearing cannot be preserved in patients in whom the tumor is intimately in contact with the cochlea, and radiation coverage of complete tumor should not be compromised in such cases. Another complication is vagal neuropathy in the form of vocal cord paralysis, albeit in anecdotal case reports.[8,22] We did not encounter any incidence of stenosis or radiation necrosis of the temporal bone. Surgical management, although once considered gold standard, has taken a back seat after long-term favorable results of radiosurgery (Table 4).

Table 3. Clinical Outcome of Patients

Symptom No.	Symptom/Signs	Before Dose Fractionated Gamma Knife Radiosurgery	After Dose Fractionated Gamma Knife Radiosurgery			
			Stable	Improved	Worse	New Onset
1	Headache	8	0	8	0	1
2	Tinnitus	7	0	7	0	0
3	Hearing loss	7	5	2	0	0
4	Dysphonia	7	2	5	0	0
5	Tongue weakness	7	7	0	0	0
6	Dysphagia	5	3	2	0	0
7	Shoulder drooping	5	5	0	0	1
8	Ear bleed/discharge	3	0	3	0	0
9	Diplopia	2	1	1	0	0
10	Facial weakness	1	1	0	0	0
11	Ataxia/dizziness	4	3	1	0	0
	Total: 110	56	27	29	0	2

Limitations

Although useful to both practitioners and patients, this study has limitations. JP is rare, and as in other studies, our population is of limited size. Neurologic deficits reported in this study (see Table 1) are patient-reported outcomes and depend on subjective experience, except hearing deficit, and facial nerve palsy. It is possible that this subjective evaluation could reflect a patient's adaptation to their deficits 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. The natural history of JP is unpredictable, and it is of interest to know if the tumor control is attributed to the benign natural course of the disease or is an effect of radiosurgery. The chances of late-onset tumor failure also need to be checked. Such patients need lifelong follow-up after treatment by any modality. Comparison of the outcome in the literature is difficult because tumor progression is ill defined. Different reported series used different criteria of volumetric progression (from 10% to 25%); hence, comparative evaluation is nonstandardized.

Another limitation of this study is the retrospective design, although the data were collected according to a fixed protocol in a prospective manner. We practice frame-based dose fractionation because the Gamma Knife ICON model is not available. We advocate that any center treating benign tumors with radiation techniques should be meticulous in their follow-up to obtain better evidence of the efficacy of the therapy. The results of this study can be used for comparative analysis with the results of volume fractionation GKS for better evidence.

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 GKS. In our opinion, patients with questionable diagnosis, young patients with brainstem compression, and patients in whom reasonable resection can be achieved with no cranial nerve injury should be offered surgical intervention; otherwise, GKS should be preferred to surgery as the acceptable primary mode of treatment.

CONCLUSIONS

GKS provides effective long-term control of glomus jugulare tumors and overall improvement or stabilization of neurologic deficit in nearly all patients. Patients with previous resection are less likely to experience improvement of neurologic deficit. It should be stressed to the patients that the lesion will remain visible on the follow-up radiology but with less volume and improved signs and symptoms. Primary GKS, either single or multiple fractions, should be considered the standard of care for JP of any size until it causes brainstem compression.

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Table 4. Review of Literature: Radiosurgery for Jugular Paraganglioma

Reference, SRS Type	Mean Age (years)	Number of Patients (Previously Intervened)	Mean TV at Treatment (cm^3)	Mean FU (months)	Prescription Dose (Mean/Median/Range of Marginal Dose) (Gy)	Tumor Control (%) (Definition of Tumor Control)	Clinical Outcomes
Patel et al., 2018,[8] GKS	54.5	60 (23)	6.8	66	16	91.7 (TV <15 growth at last FU)	New or worsened lower CN X deficit, 3.3%; salvage radiotherapy, 1
Spina et al., 2018,[16] GKS	65.6	30 (9)	7.69	91	16	96.6 (stable or decreased TV)	Clinical status unchanged in 56.6% and improved in 43.4%; tinnitus improved in all patients; transient trigeminal neuralgia, 1
Winford et al., 2017,[20] GKS	62.7	38 (4)	5.8	39.1	13.2	82 (treatment failure was defined by a TV increase >10)	Improvement in CN deficits, 18%; stable examinations, 76%; toxicity attributable to GKS, 26%. Vertigo, 4; new-onset pain, 4; dysphagia, 4
Wakefield et al.. 2017,[21] GKS	64	17 (9)	9.8	123	15	TV reduced, 59; TV same, 35; TV increase, 6	Improvement in CN V (0%), VII (67%), VIII (63%—80%), IX/X (combined 29%—50%), XI (25%), and XII (0%); overall, 53%. Stable clinical status, 41%; worsened clinical status, 6%
Ibrahim et al., 2017,[22] GKS	55	75 (28)	7	51.5	18	93.4 (TV same or decreased)	CN deficits improved, 20%; stable, 64%, new symptoms, 16%. CN X palsy, 1; transient CN VII palsy, 1
Hafez et al., 2016,[16] GKS	43.6	22 (7)	7.26	56	14.7	Tumor PFS, 95.5; TV same, 13; TV decreased, 8; TV increased, 1	CN deficits improved, 12; stable, 7. New moderate deficits, 3 (transient facial palsy, trigeminal pain, hearing loss)
Dobberphul et al., 2016,[20] GKS	62.8	12 (0)	NA	27.6	12—18	100; average change in TV, 37% decrease	Tinnitus improved, 80%. All patients with lower CN dysfunction subjectively reported that their symptoms were stable at most recent FU. Facial nerve palsy, 1
Liscak et al., 2014,[21] GKS	56	46 (31)	3.6	118	20	97.8; TV reduced, 77%,	Tinnitus improved, 49%, worsened, 4%. New CN tinnitus, 1; facial palsy with recurrence, 1

SRS, stereotactic radiosurgery; TV, tumor volume; FU, follow-up; GKS, Gamma Knife radiosurgery; CN, cranial nerve; PFS, progression-free survival; NA, not available; LINAC, linear accelerator; RRC, radiosurgery response classification.

Continues

Table 4. Continued

Reference, SRS Type	Mean Age (years)	Number of Patients (Previously Intervened)	Mean TV at Treatment (cm^3)	Mean FU (months)	Prescription Dose (Mean/Median/Range of Marginal Dose) (Gy)	Tumor Control (%) (Definition of Tumor Control)	Clinical Outcomes
Gandía-González et al., 2014,[23] GKS		58 (25)	12cc	86.4	13.6	94.8; TV decrease, 67.2; TV stable, 27.6	91.4% had clinical control with improved or stable symptoms; improvement in tinnitus, 100%; other symptoms, 34.5%; clinical worsening in 8.6%; hearing loss, 4; dysphagia, 1
Sheehan et al., 2012,[15] GKS	59	132 (59)	7.8	50.5	15	Tumor PFS at 5 years after GKS: 88% (upfront GKS); 90% (salvage GKS)	Improvement CN deficits, 11%. Tinnitus improved, 49%. New or progressive CN deficits, 15%
Chen et al., 2010,[24] GKS	60	15 (4)	7.3	43.2	14.6	80.8; TV decrease, 46.7; TV same, 33.3	8 of 9 patients with FU data showed stabilization/ improvement; dysarthria, headache, 1
Navarro Martin et al., 2010,[25] GKS	56	10 (8)	4	9.7	14	100; TV shrinkage, 20; TV stable, 80	Symptom relief (tinnitus, vertigo, dysphagia), 50%; stable symptoms in others; transient headache, 1
Gigliotti et al., 2018,[26] LINAC	65	16 (6)	11.7	44	15 in 1 fraction (n = 6); 21–30 in 3–5 fractions (n = 9) at 80% isodose line	88 (TV shrinkage or the absence of tumor growth on FU)	81.25% patients had posttreatment improvement of symptoms; others have symptom control; 7 of 9 patients with tinnitus improved; grade II vertigo, 1; hydrocephalus, 1; salvage RT, 1; salvage excision, 1
El Majdoub et al., 2017,[27] LINAC	59	32 (14)	9.5	148	15–30 at 80% isodose line	100; TV shrinkage, 12; TV stable, 15	Improvement in tinnitus (40%); CN V, VII, IX–XII weakness (38.5%); vertigo (54.5%); headache (83.3%); otalgia (75%); facial nerve palsy, 1
Tse et al., 2017,[28] LINAC	63	13 (0)	10.4	47	15–30 at 80% isodose line in 1/3/5 fractions	92.3; TV shrinkage >20 in 46.7	Tinnitus resolution, 87.5%; overall, 80% had symptom improvement; facial spasm,1; hoarseness,1; sigmoid sinus thrombosis, 1; hearing loss, 1

Schuster et al., 2016,[29] LINAC	55	14 (0)	3.78	31.7	15—18 in single fraction (n = 5); 25 in 3—7 fractions (n = 9)	92.9; TV shrinkage, 44.4; TV stable, 50	Post-SRS CN XII palsy, 1
Sager et al., 2014,[30] LINAC	55	21 (5)	NA	49	15 at 85%—100% isodose line	100 (tumor shrinkage or the absence of tumor growth on FU)	NA
de Andrade et al., 2013,[31] LINAC	58.4	15 (2)	18.5	35.4	14	No interval changes in all patients	Improved, 3; no change, 12; transient facial nerve palsy, 1
Hurmuz et al., 2013,[32] LINAC	68	14 (1)	15.8cc	39	25 in 5 fractions at 80% isodose line	100; tumor regression in 43	Complete clinical improvement in 8 patients; no toxicity reported
Lieberson et al., 2012,[33] LINAC	59	36 (11)	3—64	46.8	20 in 1—5 sessions at 80% isodose line	RRC grade 1, 50; RRC grade 2, 50 (RRC grade 1, >10 shrinkage in TV; grade 2, TV same; grade 3, TV growth)	Of 26 patients with neurologic deficits, 8 recovered entirely, 10 recovered partially, 5 unchanged; tinnitus improved in 4 of 6 patients; increased vertigo, 1, transient cranial neuropathies (tongue numbness and hearing loss, 2); salvage surgery, 1
Suárez et al., 2012[15] (review), GKS and LINAC	56.9	254 (0)	NA	41.2	NA	93.7; TV decrease, 32.3; TV stable, 61.6; TV growth, 6.3	CN deficits improved, 68.4%; CN deficits stable, 24.2%. New-onset permanent CN deficits after SRS, 7.4%; hearing improved, 3.2%; hearing loss, 6.5%
Guss et al., 2011[34] (review), GKS and LINAC	NA	335 (NA)	NA	36	NA	97 (control = unchanged or reduced TV after SRS)	95% of patients were stable or had improved clinically
Ivan et al., 2011[11] (review), GKS and LINAC	58	339 (0)	2.6	71	NA	95 (lack of documented growth)	Posttreatment CN deficits 9.7% after SRS compared with 38% after gross total resection
Present series, 2019, dose fractionated Gamma Knife radiosurgery	41.5	10 (0)	29.9	39	7.64 × 3, 11.2 × 2	100; RRC grade 1, 90; RRC grade 2, 10	Improved symptoms in 48.2%; stable symptoms in 51.8%; new-onset CN XI palsy, 1; new-onset transient headache, 1

SRS, stereotactic radiosurgery; TV, tumor volume; FU, follow-up; GKS, Gamma Knife radiosurgery; CN, cranial nerve; PFS, progression-free survival; NA, not available; LINAC, linear accelerator; RRC, radiosurgery response classification.

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