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Gamma knife radiosurgery for glomus jugulare tumors: Therapeutic advantages of minimalism in the skull base

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Context: Glomus jugulare (GJ) tumors are paragangliomas found in the region of the jugular foramen. Surgery with/without embolization and conventional radiotherapy has been the traditional management option. **Aim:** To analyze the efficacy of gamma knife radiosurgery (GKS) as a primary or an adjunctive form of therapy. **Settings and Design:** A retrospective analysis of patients who received GKS at a tertiary neurosurgical center was performed. **Materials and Methods:** Of the 1601 patients who underwent GKS from 1997 to 2006, 24 patients with GJ underwent 25 procedures. **Results:** The average age of the cohort was 46.6 years (range, 22-76 years) and the male to female ratio was 1:2. The most common neurological deficit was IX, X, XI cranial nerve paresis (15/24). Fifteen patients received primary GKS. Mean tumor size was 8.7 cc (range 1.1-17.2 cc). The coverage achieved was 93.1% (range 90-97%) using a mean tumor margin dose of 16.4 Gy (range 12-25 Gy) at a mean isodose of 49.5% (range 45-50%). Thirteen patients (six primary and seven secondary) were available for follow-up at a median interval of 24 months (range seven to 48 months). The average tumor size was 7.9 cc (range 1.1-17.2 cc). Using a mean tumor margin dose of 16.3 Gy (range 12-20 Gy) 93.6% coverage (range 91-97%) was achieved. Six patients improved clinically. A single patient developed transient trigeminal neuralgia. Magnetic resonance imaging follow-up was available for 10 patients; seven recorded a decrease in size. There was no tumor progression. **Conclusions:** Gamma knife radiosurgery is a safe and effective primary and secondary modality of treatment for GJ.

Key words: Follow-up, gamma knife, glomus jugulare tumor, stereotactic radiosurgery, surgery

Glomus jugulare tumors (GJ) are chemodectomas found in the region of the jugular foramen and extending into the temporal bone, middle ear cavity and the infratemporal fossa with frequent invasion of the adjacent jugular bulb, internal carotid artery and the lower cranial nerves. These rare tumors reportedly occur in a ratio of 1:1,000,000 in the fifth to sixth decade of life.^[1]

Time to diagnosis from the onset of the first symptom is between four and six years. Thus the neurosurgeon often confronts a very large tumor located in one of the most poorly accessible surgical regions of the anterolateral foramen magnum. Treatment is controversial. Traditional options have included surgery with/without preoperative embolization followed by postoperative conventional external beam radiotherapy. These have been associated with significant morbidity and mortality.^[2-10]

Gamma knife radiosurgery has been proposed as an alternative to conventional external beam radiotherapy as it has the capability of delivering high-dose single fraction radiation while sparing adjacent neurovascular structures. Gamma knife radiosurgery has been reportedly delivered to 192 patients worldwide.^[1,10-19] Recommendations as to whether GKS can be delivered as a *primary* form of therapy remain unclear.

This retrospective study analyzes the use of Gamma Knife Radiosurgery (GKS) as a primary or as an adjunctive form of therapy for GJ over a period of a decade.

Materials and Methods

This study was carried out at a tertiary level apex neurosurgical institute using a Leksell Gamma Knife™ (Elekta instruments AB, Stockholm, Sweden) Model B unit. A retrospective chart analysis of all patients who underwent a radiosurgical procedure with either a biopsy or classical radiological features of GJ was conducted. Classical features on radiology included a location centered on the jugular foramen, bony destruction, brilliant contrast enhancement, flow voids and the absence of a dural tail.

The stereotactic frame was placed as low, as posterior and as much to the side of the lesion as possible with the head in a position of flexion. Localizing magnetic resonance imaging (MRI) was performed using contiguous 2 mm slice thickness axial T1 weighted contrast enhanced images (TR 600 ms, TE 14 ms,

FOV-230, flip angle 90°). A stereotactic angiogram was not performed as the lesions were all clearly discernible on MRI and the attending radiologist did not perceive any diagnostic doubt. Spatial distortion was minimized by shimming. Stereotactic images were acceptable only after the inbuilt accuracy meter of the Gamma plan indicated a mean error of deviation of less than 1 mm.

The gamma plan was decided using the following safety tolerance limits - doses to the brainstem, cranial nerves and visual pathways were not to exceed 12 Gy, 20 Gy and 10 Gy respectively. The prescribed tumor margin dose was to exceed 16 Gy delivered to the 50% isodose line wherever feasible with at least 90% tumor coverage. An example of typical dosimetry has been provided in Figure 1.

The demographic profile, pre and post-treatment symptomatology, pre-treatment radiology, and radiation-related parameters and planning were reviewed. Clinical follow-up records were collated and patients were telephonically interviewed to assess the current clinical status. Magnetic resonance imaging was carried out ordinarily at 12 months post-treatment or earlier if so clinically indicated.

Of the 1601 patients who underwent GKS from 1997 to 2006, 24 patients with GJ underwent 25 procedures. The average age of the cohort was 46.6 years (range, 22-76 years) and the male to female ratio was 1:2. The most common neurological deficit was IX, X, XI cranial nerve paresis (15/24). Sensorineural deterioration in hearing, facial paresis, XIIth cranial nerve paresis and trigeminal sensorimotor impairment were also observed (Table 1). It was noted that of the 12 patients with VIIth cranial nerve involvement, all four who underwent a major surgical exploration and biopsy prior to GKS developed at least a Grade V/VI House and Brackman facial palsy (Table 2). A single patient received previous conventional radiotherapy.

Of the 25 tumors that underwent GKS, mean tumor size was 8.7 cc (range, 1.1-17.2 cc). The coverage achieved was 93.1% (range 90-97%) using a mean tumor margin dose of 16.4 Gy (range 12-25 Gy) delivered to a mean isodose of 49.5% (range 45-50%) using an average of nine isocenters (range 2-17). A single patient received GKS therapy twice, though the tumor size was marginally reduced, as metabolic imaging revealed viable tumor and the operating surgeon was wary of the biological aggressiveness of the lesion which had mandated five surgeries and conventional radiotherapy in the past. Fifteen patients underwent primary GKS. Of the 14 patients with any hearing, the point dose to the cochlea was an average of 3.6 Gy. No patient reported a deterioration in hearing on follow-up.

Thirteen patients had a follow-up of at least six months with a median interval of 24 months following GKS (range 7-48 months). The average tumor size was 7.9 cc (range 1.1-17.2 cc). Using a mean tumor margin

dose of 16.3 Gy (range 12-20 Gy) delivered at a 50% isodose, 93.6% coverage (range 91-97%) was achieved. Six patients received primary GKS. Overall, six of these 13 patients improved clinically.

Magnetic resonance imaging follow-up was available for 10 patients. Seven recorded a decrease in size (Figure 2A, B). There was no tumor progression observed in any case. We analyzed the results of patients who received primary and secondary GKS separately (Tables 3 and 4). The main differences between the two groups were in tumor size and margin dose. In the primary GKS group, mean tumor size was 6.8 cc and 93.4% coverage was achieved using a mean tumor margin dose of 17 Gy. In the secondary GKS group, mean tumor size was 9.2 cc and 93.2% coverage was achieved using a mean tumor margin dose of 15.8 Gy. These did not reach statistical significance using the T-test.

Only one complication was noted with a single patient developing trigeminal neuralgia three months after primary GKS.

Table 1: Neurological deficits prior to treatment

Neurological deficit	Total number
IX, X, XI	15/24
VIII	13/24
XII	12/24
VII	12/24
V	2/24
Ataxia	3/24
Pulsatile tinnitus alone	2/24
Asymptomatic	1/24

Table 2: Comparative analysis of facial palsy in the post surgical cohort

House and Brackman facial palsy grade	Primary GKS (n = 6)	Secondary GKS (n = 6)
Grade V & VI	0	4
Grade II	6	2*

*One patient underwent only preoperative partial embolization

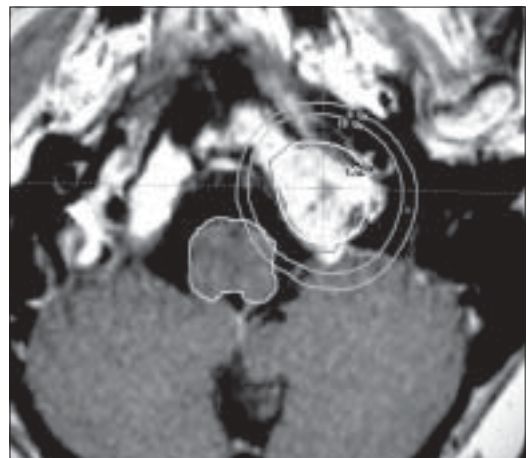


Figure 1: Gamma plan dosimetry. The 20 Gy isodose line (innermost line hugging the tumor) covers most of the tumor. The 10 Gy isodose line (inner of the two concentric circles) barely touches the surface of the brainstem, which is separately outlined

Table 3: Follow-up chart for patients undergoing primary gamma knife radiosurgery

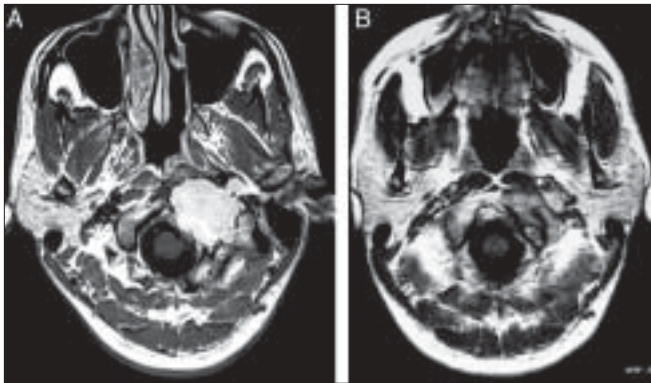
S. no	Date	Age (years)	Mean tumor size (cc)	Coverage (%)	Mean tumor margin dose (Gy)	Follow-up (months)	Clinical condition	Tumor size
1.	2002	56	2.8	95	12	17	Voice better	Same
2.	2002	39	4.5	93	15	48	Voice and ataxia better	Decreased
3.	2003	52	1.5	96	20	33	Same	Decreased
4.	2004	45	1.1	97	15	20	Voice better	NA*
5.	2004	63	7.9	91	20	14	Trigeminal neuralgia	Decreased
6.	2004	22	12.6	91	19	13	Voice better	Decreased
7.	2004	36	17.2	91	18	22	Same	Decreased

*NA - MRI not available

Table 4: Follow-up chart for patients undergoing secondary gamma knife radiosurgery

S.no	Date	Age (years)	Mean tumor size (cc)	Coverage (%)	Mean tumor margin dose (Gy)	Follow-up (months)	Clinical condition	Tumor size
1.	1997	42	11	93	12	24	Tinnitus and ataxia better	NA*
2.	2002	40	2.8	93	20	30	Voice and tinnitus better	Decreased
3.	2003	46	8.9	96	15	42	Same	NA*
4.	2003	63	6.4	92	15	7	Same	Same
5.	2003	54	16	94	15	36	Same	Decreased
6.	2003	41	10.2	95	18	34	Same	Same

*NA - MRI not available

**Figure 2: (A) Pre Gamma Knife stereotactic contrast enhanced MR image of a patient with a large 17.3 cc tumor involving the left lateral mass of the atlas. (B) Contrast enhanced MR image of the same patient 22 months after GKS showing tumor regression**

Discussion

Glomus jugulare tumors are indolent, slowly growing, locally destructive lesions located in one of the most poorly accessible surgical regions of the skull base. The operative approach is, in addition, complicated by the fact that lesions may be both intra and extradural with engulfment of critical neurovascular structures such as the internal jugular vein, the internal carotid artery, the vertebral artery, the lower cranial nerves, the Eustachian tube and the middle ear. The tumor is frequently highly vascular and merits preoperative embolization.

Thus, it is not surprising that resection entails a great deal of morbidity, not infrequent mortality and leaves behind large residual tumors.^[2-5] In our series, of the

eight patients who underwent a surgical resection, five (63%) developed a Grade V/VI House and Brackman facial palsy. The postoperative residual tumor volume ranged from 2.8 to 17 cc with a mean of 10.5 cc.

GJ - Radiosensitive or radioresistant?

Traditionally, conventional, fractionated, external beam radiotherapy was used to treat residual tumors with varying degrees of success ranging from a maximum of 61-71% to an average of 23%. Side-effects include osteoradionecrosis of the temporal bone, radiation necrosis of the temporal lobe, mastoiditis and second malignancies.^[6-10] Although the glomus cells per se are radioresistant, radiotherapy helps halt tumor growth by inducing fibrosis around the supplying vessels.^[10] Stereotactic radiosurgery with the Gamma knife system delivers precise high-dose radiation to a small localized field to increase the chances of obliterative endarteritis while reducing complications by sparing adjacent normal structures.

GKS - Efficacy and safety

Gamma knife radiosurgery has been noted to have especially good control rates for GJ tumors.^[1,10-19] In one of the earliest multicenter studies, 47 patients at six European sites were evaluated at a median of 24 months after GKS.^[1] The median tumor volume was 5.7 cc with 16.5 Gy delivered on an average to the tumor margin. Control rates were 100% and 40% of tumors regressed on follow-up with an overall 5.8% risk of complications.

In our series, a 100% control rate has been observed at a median follow-up of two years. Though the median

Table 5: Comparative gamma knife series 1999-2007

Year	Series	Patients	Mean tumor size (cc)	Mean tumor margin dose (Gy)	Follow-up (months)	Regression rate %	Progression rate %	Adverse effect %
1999	Liscak <i>et al.</i> ^[1]	66	5.7	16.5	24	40	-	5.8
2000	Jordan <i>et al.</i> ^[10]	8	9.8	16.3	20	56	-	12.5
2004	Pollock <i>et al.</i> ^[12]	42	13.2	14.9	44	31	2	15
2005	Sheehan <i>et al.</i> ^[13]	8	6.2	15	32	56	-	-
2006	Varma <i>et al.</i> ^[14]	17	6.9	15	48	47	23	11.8
2006	Gerosa <i>et al.</i> ^[15]	20	7.0	17.3	51	40	5	10
2007*	Current series	13	8.7	16.4	24	70	-	7.6

*Of the 13 patients, 10 patients had a post gamma knife MRI of whom seven recorded a decrease in size. A single patient of the 13 with clinical follow-up reported ipsilateral trigeminal neuralgia

follow-up period is only 24 months, it is important to note that 70% of patients (7/10) with available MRI follow-up had tumor regression. Of the three patients with no follow-up MRI, two patients had noted an improvement in clinical symptoms. This compares favorably with other large single-institutional series from the Cleveland and Mayo Clinics (Table 5).^[12,14]

Only one complication was noted - a single patient of the 13 with clinical follow-up (7.6%) developed trigeminal neuralgia in the V2 and V3 distributions three months after primary GKS for a 7.9-cc tumor. She received 20 Gy of radiation to an isodose of 50%. The follow-up MRI denoted a decrease in tumor size, with no evidence of radiation changes to the brainstem. The Gamma plan was reviewed and it was found that the brainstem received radiation in the upper range of the normal tolerance dose (12 Gy). The safety tolerance of the Vth Nerve complex was not exceeded. Gamma plans are now devised to ensure that no part of the brainstem receives more than 11 Gy of radiation which is now the upper limit of the normal safety tolerance dose in our center. We would rather compromise on the tumor marginal dose than risk neurological complications as our series indicates that a tumor margin dose in excess of 16 Gy is sufficient to produce a 100% control rate. However, we would attempt to keep the tumor margin dose greater than 15 Gy as a study using volumetric data revealed that four of 17 patients treated with the same had recorded an increase in tumor size at last follow-up.^[14]

Long-term results of GKS

Glomus jugulare tumors are benign tumors. A minimum follow-up of 10 years is a must to accurately assess control rates. The glomus cells are radioresistant and may behave unpredictably with time. Yet, an Austrian study of 18 patients revealed tumor control rates of 94.7% (seven cases with decreased and 11 with stable tumor size) at a median observation time of 7.2 years. There was only one case of tumor progression which required redo GKS at 85 months. The median tumor volume was 5.2 cc and the marginal dose was 14 Gy at an isodose of 50%.^[11] In our series, the tumor volume was larger and the marginal dose was higher with a 70% early tumor regression rate. Extrapolating

these results suggests that GKS may produce satisfactory long-term results if the radiation dose is adequate.

GKS - A primary treatment modality of GJ?

This data provokes a controversial question: is Gamma knife radiosurgery perhaps the best option for the *primary* treatment of glomus jugulare tumors? Our data indicates that 83% of patients who underwent primary GKS had tumor regression on MRI as opposed to 50% of patients who underwent GKS as an adjunctive procedure. The latter cohort also had an 80% incidence of a Grade V/VI facial palsy.

The possible exceptions to gamma knife therapy would be the presence of a diagnostic dilemma, patients presenting with raised pressure symptoms, tumor volume exceeding 19-cc tumor extension below the second cervical vertebra in a patient with a large skull or close proximity to the brainstem precluding the delivery of an adequate tumor margin dose.

In a benign disease, tumor control and quality of life indices would appear to be more significant than eradication and morbidity. Whereas surgery is associated with a higher morbidity, the overall quality of life appears to be significantly better with GKS as a primary modality of therapy.^[16] Though a cautioning factor does remain that the long-term results after GKS are unknown, tumor recurrences if at all can also be dealt with using a second procedure, with a minimal complication rate.^[11]

Conclusion

Gamma knife radiosurgery is a safe and effective modality of treatment for glomus jugulare tumors. Marginal doses of 16 Gy to an isodose of 50% with tumor coverage exceeding 93% resulted in a 100% tumor control and 70% tumor regression rate at 24 months follow-up. Gamma knife radiosurgery may be a safe and effective option for the primary treatment of glomus jugulare chemodectomas.

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