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Research Article

Outcome of Gamma Knife Radio Surgery in the Treatment of Tumor-Related Symptomatic Trigeminal Neuralgia: Our initial experiences from National Institute of Mental Health and Neurosciences (NIMHANS)

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Abstract

Introduction: Symptomatic trigeminal neuralgia sometimes occurs secondary to intracranial skull base tumor. GKRS has been reported as a potential treatment option for tumor-related trigeminal neuralgia. However, there is paucity of literature from India on the clinical outcome of GKRS for symptomatic trigeminal neuralgia.

Aims and Objectives: The primary objective of this study is to evaluate the efficacy and safety of Gamma Knife Radio Surgery with respect to relief of facial pain and tumor control in patients of tumor related

trigeminal neuralgia and to identify predictive factors of outcome.

Material and Methods: This is a retrospective study of patients with tumor related trigeminal neuralgia, evaluated and treated with Gamma Knife Radio Surgery at the National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore since March 2006 to June 2013 with minimum of 6 months of follow up. Medical case records and images were reviewed. Pain intensity at the time of diagnosis/treatment and at follow up after GKRS was quantified using the Barrow Neurological Institute (BNI) criteria.

Results and Observations: Sixty-seven patients were treated for tumor with trigeminal neuralgia during the study period. 60 patients were included in the study. The most common tumor was vestibular schwannoma 27(45%), followed by meningioma 23(38.33%), trigeminal schwannoma 9(15%) and cavernous sinus hemangioma 1(1.67%). The mean follow up duration was 35.4 months (range, 7-70 moths). The mean tumor volume was 4.4 cc and mean radiation dose was 12.7 Gy. Onset of initial improvement of pain was achieved in a mean duration of 21 days. There was 46.7% BNI-I pain control, 43.3% BNI-II, 5% BNI-III and 5% BNI –IV/V. Post GKRS tumor volume reduction has significant ($p < 0.05$) correlation with good pain control. Higher treatment dose is correlated with good pain control.

Conclusion: Excellent pain control and tumor control with better quality of life is possible with a minimally invasive fashion using Gamma Knife Radio Surgery. Primary Gamma Knife Radio Surgery can be considered as a preferable therapeutic option in carefully selected patients with tumor related symptomatic trigeminal neuralgia.

Keywords: BNI (Barrow Neurological Institute); Gamma Knife Radio Surgery (GKRS);

Introduction

Facial pain is a common symptom among patients referred for neurosurgical consultation. Trigeminal neuralgia is the commonest craniofacial pain syndrome. Trigeminal neuralgia sometimes occurs secondary to intracranial skull base tumor or other pathology located in and around the trigeminal nerve and its ganglion (symptomatic trigeminal neuralgia). Gamma Knife Radio Surgery (GKRS) has been reported as a potential treatment option for tumor-related symptomatic trigeminal neuralgia. However, there is paucity of literature on the clinical outcome of GKRS for symptomatic trigeminal neuralgia [1-5].

Published studies on tumor-related facial pain lack standardization in grading the pain response to treatment. To standardize grading of pain response, Sarah., *et al*. [5] defined pre- and post-GKRS pain based upon the BNI (Barrow Neurological Institute) Pain Intensity Scores [6] generally used for idiopathic trigeminal neuralgia. Another system, the Excellent-Good-Fair-Poor (EGFP) categorical scale adopted by Mayo Clinic has also been used in quite a few studies [3,4].

Gamma Knife Radio surgery (GKRS) was started in National Institute of Mental Health and Neurosciences (NIMHANS) in the 2006. Many patients have been treated with GKRS since the inception. In this study we have evaluated our initial experiences with GKRS in treatment of tumor related symptomatic trigeminal neuralgia in Indian patients.

Aims and Objectives

The primary objective of this study is to evaluate the efficacy and safety of Gamma Knife Radio Surgery with respect to relief of facial pain and tumor control in patients of tumor related trigeminal neuralgia and to identify predictive factors of outcome.

Material and Methods

This is a retrospective study conducted in the year of 2013 in National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore following clearance from the Institutional Scientific Ethics Committee (Ref No. NIMHANS IEC Sl.No.2, Clinical Neurosciences). NIMHANS Gamma Knife Registry was searched for patients with skull base tumor with GKRS between March 2006 and June 2013. Medical case records and images were reviewed for each of these patients. Pre GKRS clinical details were collected from the case files and GKRS plan. Relevant information was obtained from the patients with either telephonic conversation or a personal interview in subsequent follow up visit to the hospital. Pain intensity at the time of diagnosis/treatment, subsequent follow up after GKRS and at the time of pain relapse (if any) was quantified using the Barrow Neurological Institute (BNI) criteria.

Serial follow up MRI was reviewed for tumor status (decreased, increased or status quo) and correlated with the trigeminal neuralgia pain score (BNI score). A change in tumor size at the last imaging was classified as a change of 2 mm or more in any of the three dimensions compared to imaging at the time of GKRS [4,5,11].

Patient's characteristics were expressed in terms of mean, standard deviation, 95% CI, minimum and maximum values. To examine the correlation of various factors that might predict pain relief, spearman's rho as well as chi square test was performed. Value of $p < 0.05$ was considered as significant.

Exclusion criteria

- Patients with a history of brain radiation or intracranial surgery for their tumor prior to GKRS or GKRS for residual lesion.
- Patients lost to follow up
- less than 6 months of follow up
- Patients with incomplete or inadequate data
- Patients with confounding pre-existing neurological illness such as demyelinating disease (viz. multiple sclerosis), brain stem stroke affecting central trigeminal pathway

Results and Observations

Sixty-seven patients were treated for skull base or posterior fossa lesion with trigeminal neuralgia during March 2006 to June 2013. 60 patients were included in the study after excluding seven patients as per exclusion criteria. The Mean age of the patient was 48 years ranging from 18-70 years. Twenty-one (35%) patients were male, and 39 (65%) patients were female. The male to female ratio was 1:1.85. Twenty-four (40%) has left side pain and the mean duration of pain before GKRS was 16.8 months (range, 1-108 months). Seven patients (11.6%) had BNI score III and 53 patients (88.4%) had BNI score IV/V at the time of GKRS. Majority of patients had neuralgic pain involving multiple division of trigeminal nerve;

only 5 patients had isolated facial pain restricted to V3 division. Twenty-one (35%) patients had facial numbness at presentation prior to GKRS. The mean follow up was 35.4 months (range, 7-70) with 95% CI 31.1-39.7 month.

Most common tumor in the study was vestibular schwannoma 27(45%), followed by meningioma 23(38.33%), trigeminal schwannoma 9(15%) and cavernous sinus hemangioma 1(1.67%). Meningioma was in the cavernous sinus for three patients while in 20 patients' meningioma was in the posterior fossa (Petro clival area, cerebellopontine angle or tentorial). The mean tumor volume was 4.4 cc ranging from 0.85cc to 11.3 cc.

Onset of initial improvement of pain was achieved in a mean duration of 21 days (range, 3-45 days) and 95% CI 18.2-23.6 days. As per the last follow up, (n = 60) there was 46.7% BNI-I pain control, 43.3% BNI-II, 5% BNI-III and 5% BNI –IV/V. As the GKRS started only in 2006, there was only few patients (n = 6) with long term (> 5 years of follow up). Among the cohort of 60 patients, at least 31 patients had followed up of 3 years. At the end of three years, 15 patients (48.4 %) had BNI score I, 14 patients (45.2%) had BNI score II, one patient (3.2 %) had BNI score III while one patient (3.2%) had BNI score IV/V pain relief. Collectively at 3 years follow up, 96.8% patients had excellent pain control and 93.6% were off medication. There were only 6 patients (10%) who had a follow up of more than 5 years. Among these patients, 4 patients (66.6%) had BNI score II, one patient (16.7%) had BNI score III and one (16.7%) had BNI score IV. Good tumor control rate was recorded as none of the patients had increase in tumor size. Tumors decreased in size as per the last follow up MRI in 51(85%) patients while in 9(15%) patients; there was no change in the tumor volume.

We observed that post GKRS tumor volume reduction has significant (p 0.0001) correlation with good pain control. It is also observed that higher treatment dose is correlated with good pain control (p 0.0007). One of the patients (1.7%) has flare up of pain with transient numbness of ipsilateral face, which resoled with medical management.

One of the patients had undergone microsurgery for recurrent pain within one year of GKRS.

Discussion

Gamma Knife Radio Surgery has been reported as a treatment option for tumor-related trigeminal neuralgia and as an alternative to surgical resection [2-5]. Very few studies are available addressing the treatment of tumor-related facial pain with radio-surgery [2-5,11]. There is lot of heterogeneity in the published literature, as some of the studies included both benign as well as malignant tumor while few studies addressed only pain outcome and some addressed tumor control along with pain [4,5,7,10,11]. Pain scale is also heterogeneous in different studies [2-5]. Available literature also lacks larger patient sample and longer follow up [2-5]. The largest study sample is reported by Regis., *et al*. constituting of 53 patients; however, there was heterogeneity in terms of tumor characteristics and the radio surgical planning [10]. Our study includes large numbers of homogenous group of tumors (benign, n = 60) and homogeneous radio surgical planning. Our study addresses both tumor control and pain control following primary GKRS therapy for symptomatic tumor related trigeminal neuralgia and analyzed the various predictive factors of treatment related outcome.

Three issues are widely debated and addressed, by most of the authors in treatment of tumor related TN with stereotactic radio surgery

- Radio surgical approaches
- Pain relief and
- Tumor control.

In our study tumor was the primary target for GKRS in all the patients. The median dose of radiation was 12 Gy (range, 11-22) at 50% isodose line. This agrees with all other available studies [2-5]. We feel that radiation dose of 12 Gy at 50% isodose line is optimum in these setting; however, dose can be tailored to suit individual patients based on the tumor volume, type and pathological anatomy.

In our study the tumor control rate was 100% as none of the tumor increased in size. In fact, in 85% of patients the tumor size had documented decrease in the tumor volume. Our tumor control rate is like the trend available literature, which ranges from 88% to 100% [10,11].

In our study, excellent pain control without medicine was achieved in 90% of cases and overall, 95% of patients were pain free (includes 5% of patient in BNI III) at mean follow up of 35.4 months. Our pain control rates are a bit better than most of the

published series, however, not very different from the study by Young., *et al*. [2]. They also reported pain relief rate of 96%. Even looking at the pooled data of 31 patients, who had followed up more than 3 years, the excellent pain control (includes BNI I, II and III) rate was 96.8%. However, at the 5 years of available follow up, only 83.4% of patients were pain free. Though there is definitive decline in the pain control, but this is only reflection of limited available data, as our GKRS system was instituted only in 2006 and only 6 patients had completed follow up of more than 5 years. Whether this drop in pain control (though not very significant) reflects true recurrence of pain of neuropathic origin or mere reflection of skewed data of those 6 patients with longer follow up who might be having persistent or recurrent pain, need to be evaluated at a longer follow up.

On analyzing various factors to determine their predictive value with respect to post-GKRS pain relief, higher radiation dose (p 0.007) and tumor-volume reduction (p 0.0015) had a significant correlation with good pain control. In the study from Mayo clinic [11] a similar trend was reported towards higher radiation dose achieving greater pain relief. Sarah., *et al*. [5] found similar trend towards improved pain relief with tumor shrinkage over time. Similarly, Huang., *et al*. [4] believed that tumor shrinkage correlated with relief of trigeminal pain. Our study further supports the concept that the tumor is primarily responsible for trigeminal neuralgia in these cases secondary to their strategic location and distortion of trigeminal nerve/pathway. GKRS targeted toward the pathology directly yields an excellent pain control in harmony with the tumor control in properly selected cases.

Radio surgery is considered safe with low complication rate. Cranial nerve morbidity, such as new onset facial numbness, is rarely seen in groups being treated with radiosurgery for skull base tumors [4,10,14]. We had an experience of one patient having transient numbness of ipsilateral face, which resolved over time.

Pain relief procedure (MVD/rhizotomy) may be an appropriate therapeutic option for relief of pain following recurrence, especially if the tumor is responded (volume reduction) to the GKRS. This has been our experience in one of the patients with MVD and by other authors in respect to MVD and rhizotomy [4,11]. Repeat GKRS is another good option, which again can be used as pain relieving procedure, when trigeminal nerve is targeted [11]. Microsurgery for tumor resection and repeat GKRS for the tumor remains a viable option and need to be exercised with caution in properly selected cases.

Our findings need to be interpreted with caution because of some limitations. Being a retrospective study, it has limitation of recall bias. We have a relatively short median follow up time.

Pain score (Class)	Definition
I	No pain and taking no medication
II	Occasional pain, but taking no medication
III A	No pain, but taking medication
III B	Pain present, but adequately controlled with medication
IV	Pain improved, but not adequately controlled with medication
V	No relief

Table 1: The Barrow Neurological Institute pain score.

Pain score (class)	Definition
Excellent	Complete pain relief without medication
Good	Complete pain relief with medication
Fair	>50% pain relief
Poor	<50% pain relief

Table 2: Excellent-good-fair-poor categorical scale.

Title	Mean	95% CI	SD	Minimum	Maximum
Duration of symptoms (months)	16.8	11.6-22.0	20.1280	1	108
Follow up in months	35.4	31.1-39.7	16.7234	7	70
Age in years	48	45-51	12.03	18	75
Onset of pain improvement (days)	21	18.2-23.6	10.3967	3	45
Tumor volume (cc)	4.4	3.6-5.1	2.9916	0.85	11.3
Treatment dose in Gy	12.7	12-13	1.5662	11	22
Post GKRS tumor reduction (%)	26.1	20-32	22.6971	1	93

Table 3: Patient and tumor characteristics.

BNI	6m	12m	24m	36m	60m
I	48 (80%)	49(86%)	35(72.9%)	15(48.4%)	
II	11(18.3%)	6(10.5%)	11(22.9%)	14(45.2%)	4(66.7%)
III	1(1.7%)	1(1.8%)	2 (4.2%)	1(3.2%)	1(16.7%)
IV/V		1(1.8)		1(3.2%)	1(16.7%)
TOTAL	60	57	48	31	6

Table 4: Follow up duration vs. BNI score.

Factors	rho	P value
Tumor volume	0.477	0.0001
Treatment dose	-0.426	0.0007
Post GK tumor volume	0.401	0.0015
Pain type	0.435	0.7412

Table 5: Correlations (Spearman's Rho) between predictive factors of outcome and post GKRS pain relief.

DISTRIBUTION	Numbers of patients	% (n = 60)
V3	5	8.33%
V2V3	30	50%
V1V2	8	13.33%
V1V2V3	17	28.33%

Table 6: Distribution of pain.

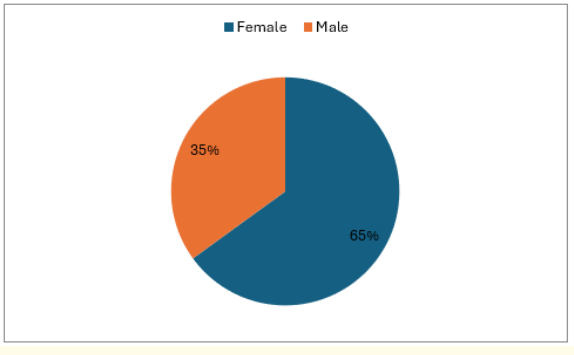

Figure 1: Gender distribution.

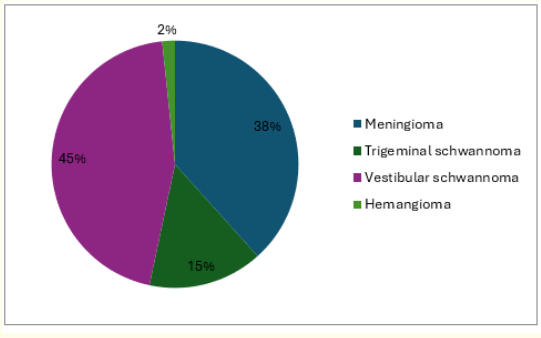

Figure 2: Tumor type.

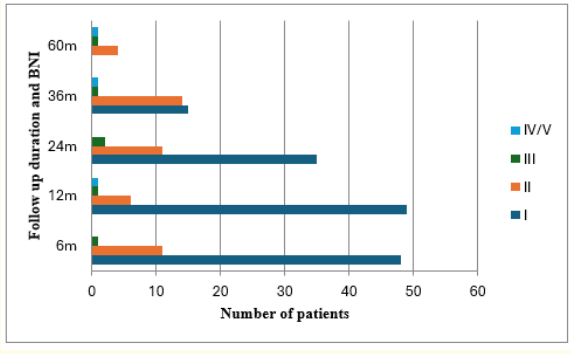

Figure 3: Bar diagram showing numbers of patients vs. BNI score in different follow up duration.

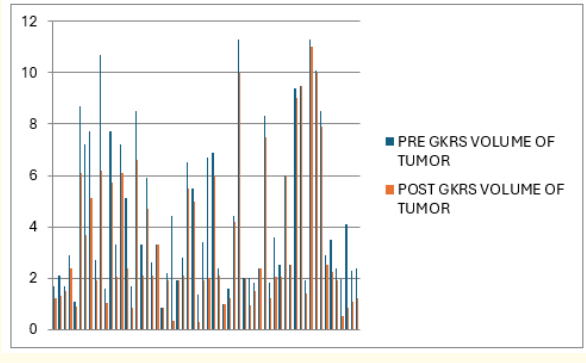

Figure 4: Graphical depiction of pre GKRS vs. post GKRS tumor volume.

Conclusion

Gamma Knife Radio Surgery is a good, effective and safe therapeutic option to treat tumor related trigeminal neuralgia. Excellent pain control and tumor control with better quality of life is possible with a minimally invasive fashion using Gamma Knife Radio Surgery. Primary Gamma Knife Radio Surgery can be considered as a preferable therapeutic option in carefully selected patients with tumor related trigeminal neuralgia.

Further larger and long-term prospective study is necessary to elucidate the best management strategy for symptomatic trigeminal neuralgia.

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