

Anatomical Considerations in Gamma Knife Radiosurgery for Idiopathic Trigeminal Neuralgia

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Objective : The authors conducted this study to present the long-term treatment outcomes (minimum 2 years) of Gamma knife radiosurgery(GKS) for trigeminal neuralgia(TN) and to demonstrate the correlation of treatment outcomes and the anatomical characteristics of TN.

Methods : From 1997 to 2003, 44 consecutive patients suffering from medically intractable pain underwent GKS for TN. A single 4mm collimator was used with a median maximum dose of 80Gy (range 75-80Gy) prescribed to the root entry zone of the trigeminal nerve. Median follow up duration was 30 months (range 24-78 months). Anatomical measurements of trigeminal nerve in magnetic resonance images during GKS planning were correlated with clinical outcome.

Results : Twenty-two patients (50%) achieved an excellent outcome (BN grade I & II), 20 patients (45.5%) a good outcome (grade IIIa & IIIb), and only 2 patients (4.5%) a poor outcome (grade IV & V). Eleven patients (25.0%) experienced pain recurrence after initial pain relief. Smaller volume of trigeminal nerve area irradiated more than 40Gy was significantly correlated with excellent outcome in both univariate and multivariate analyses respectively (P=0.033 and 0.040).

Conclusion : Anatomical considerations during the planning of GKS would be helpful for predicting clinical outcome in TN.

KEY WORDS : Trigeminal neuralgia · Gamma knife radiosurgery · Long-term outcomes · Anatomical Characteristics.

Introduction

Recently a great variety of alternative modality has been attempted for treatment of trigeminal neuralgia(TN). Among them Gamma knife radiosurgery(GKS) may have a role as an alternative treatment in intractable TN patients with a poor general condition or with an unwillingness to undergo invasive procedures. The first radiosurgical treatment of TN was performed by Leksell in the early 1950s¹⁰. However, experiences of Gamma knife radiosurgery(GKS) for TN had been reported only after 1990s^{5,8,17,22,23}. Although GKS has emerged as a minimally invasive mode of treatment for TN with few complications^{9,12,19,21,23}, questions remain about its efficacy, safety, and durability²⁰. Moreover little study has been conducted concerning the anatomical characteristics of GKS for TN. Therefore here, we report on our experiences

of GKS for the treatment of TN in 44 consecutive patients related to their anatomical characteristics in GKS planning.

Materials and Methods

Patient population

Between 1997 and 2004, 44 consecutive patients suffering from medically intractable idiopathic TN, excluding cases of secondary TN related with a tumor, multiple sclerosis, etc., underwent GKS. The study cohort was composed of patients who were unwilling to undergo more invasive interventions such as MVD, nerve block, or radiofrequency rhizotomy or who had already experienced refractory pain after these interventions. There were 12 men (27.3%) and 32 women (72.7%). The median age at GKS was 66 years (range; 37-86), and median duration of pain was 66 months (range 1 to 276). Me-

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dian follow-up period was 30 months (range; 24–78). The pain characteristics of the study subjects are summarized in Table 1.

Radiosurgical techniques and imaging parameters

Radiosurgical procedures were performed at a single center (Seoul National University Hospital, Gamma Knife Center) using a Leksell Gamma Knife Model B2 unit (Elekta Instruments, Norcross, GA, USA). All patients were treated using one isocenter. In each case, the root entry zone of the trigeminal nerve was targeted so that the 30% isodose surface contacted the edge of the pons (Fig. 1). Treatment planning was performed using the Leksell GammaPlan (Elekta AB, Stockholm, Sweden). Target localization was achieved using magnetic resonance imaging (MRI) performed on a GE Horizon Signa 1.5 tesla unit with a T1-weighted three-dimensional spoiled gradient (SPGR) of 1.0mm slice thickness and fast-spin echo T2-weighted sequence of 1.5mm slice thickness. Maximum doses of 75 (4 patients) and 80 (40 patients) Gy were delivered through a 4-mm collimator helmet. The output factor was 0.86.

Patient evaluations

All patients were subject to direct clinical follow up at one-month postoperatively and subsequently at two or three month intervals.

If a clinical appointment was missed, a telephone interview was conducted by a physician. Patients were asked to describe their pain outcomes, which were classified using the Barrow Neurologic Institute (BNI) pain outcome scale⁽⁹⁾; Grade I : no pain, no medication required, Grade II : occasional pain, no medication required, Grade IIIa : no pain, continued use of medication, Grade IIIb : some pain, adequately controlled on medication, Grade IV : pain improved but not adequately controlled by medication, Grade V : no pain relief. Grade I and II were categorized as an excellent outcome, Grade IIIa and IIIb as a good outcome, and Grade IV and V as a poor outcome. Patients were also evaluated concerning time

Table 1. Pain characteristics of the 44 patients who underwent Gamma knife radiosurgery (GKS) for idiopathic trigeminal neuralgia (TN)

Parameter	Value
Side of pain	
right	26 (59.1%)
left	18 (40.9%)
Median duration of pain (range)	66 months (1–276)
Distribution of pain	
V1 only	4 (9.1%)
V2 only	10 (22.7%)
V3 only	14 (31.8%)
V1 and V2	3 (6.8%)
V1 and V3	3 (6.8%)
V2 and V3	6 (13.6%)
V1, V2 and V3	(9.1%)

interval to initial response, medications taken for pain relief, the presence or absence of new post-GKS facial sensory impairment. Time to initial pain relief was defined as the interval between the day of GKS and the first day of pain reduction noted by a patient. Time to maximal pain relief was defined as the postoperative time required to first reach maximal improvement. Anatomical measurements were performed on the basis of magnetic resonance images using tools equipped in PACS system.

Statistical analysis

Statistical evaluations were performed using commercially available statistical software (SPSS version 10.0, SPSS Inc.). Descriptive statistics were computed using standard methods of calculating median or mean values. Univariate and multivariate analyses were performed to assess variables predictive of a pain-relief outcome and pain recurrence after GKS. For group comparisons of categorical data (nominal data or ordinal data), the two-tailed Fisher's exact test and Pearson's chi-square test were used. The unpaired Student t-test was used for continuous variables. In all cases, two-tailed probability values were calculated and statistical significance was defined as a probability value of less than or equal to 0.05.



Fig. 1. This picture depicts Gamma knife radiosurgery targeting for trigeminal neuralgia. The root entry zone of the trigeminal nerve was targeted so that the 30% isodose surface contacted the edge of the pons. The circle represents the 30% isodose curve. (A : Axial image, B : Sagittal image, and C : Coronal image).

Results

Pain outcomes

Pain response rates after GKS according to the BNI pain outcome scale, are summarized in Fig. 2. In brief, 22 patients (50.0%) achieved an excellent outcome (Grade I and II), 20 patients (45.5%) a good outcome (Grade IIIa and IIIb), and 2 patients (4.5%) a poor outcome (Grade IV and V). In other words, 50% of patients were able to do without medication and 45.5% of patients were on reduced medication. Median time to onset of initial pain relief was 14 days (range; 1~360), and median time to maximal pain relief was 4 months (range; 1-24).

Anatomical characteristics of the affected trigeminal nerve

The median length of the nerve from pons to Meckel's cave was 9.1mm (range; 3.2~16.3). The median width of the nerve was 2.8mm (range; 1.2~4.8). The width of the nerve was mea-

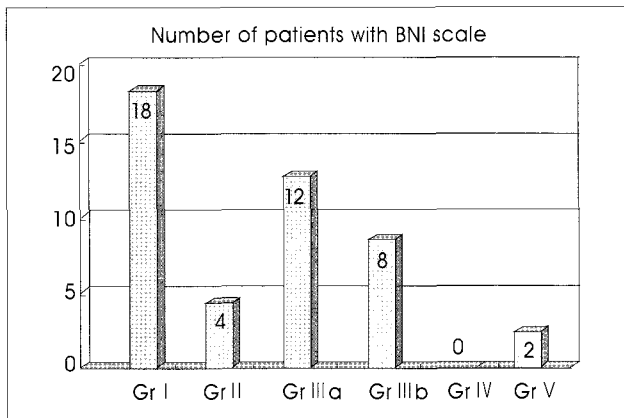


Fig. 2. Pain outcomes after Gamma knife radiosurgery for trigeminal neuralgia (BNI = Barrow Neurologic Institute, Gr = grade).

Table 2. Results of univariate and multivariate analyses of anatomical factors associated with an excellent outcome and pain recurrence after Gamma knife radiosurgery(GKS) for trigeminal neuralgia

Factors	P value	
	Univariate	Multivariate
Excellent outcome		
longer nerve length (≥ 9 mm)	1.000	NI
narrower nerve width (< 3 mm)	0.215	0.168
smaller nerve volume (< 50 mm ³)	1.000	NI
the smaller volume of irradiated more than 40Gy (< 25 mm ³)	0.033*	0.040*
Recurrence		
shorter nerve length (< 9 mm)	0.194	0.246
wider nerve width (≥ 3 mm)	1.000	NI
larger nerve volume (≥ 50 mm ³)	0.169	0.450
the larger volume of irradiated more than 40Gy (≥ 25 mm ³)	0.728	NI

(* P<0.05, NI = not included in multivariate analysis)

sured by the maximal width of the nerve. The median volume of the nerve from pons to Meckel's cave was 50.7mm³ (range; 5.7~100.2). The median volume of the trigeminal nerve irradiated more than 40Gy was 24.6mm³ (range; 4.9~ 51.1). This volume was in inverse proportion to the radiation dose irradiated to the constant volume. The median distance from the center of target to pons was 3.6mm (range; 2.6~5.7). The median volume of the pons irradiated more than 18Gy was 19.4 mm³ (range;10.1~36.5).

Anatomical factors associated with an excellent outcome or pain recurrence

In this study, several anatomical factors of an excellent outcome or pain recurrence were considered (Table 2). Among anatomical factors, only the volume of the nerve irradiated more than 40Gy was correlated with an excellent outcome with statistical significance on both univariate and multivariate analyses (P=0.033 and 0.040, respectively).

Recurrences and complications

Eleven patients (25.0%) experienced pain recurrence after initial pain relief. Median time from GKS to pain recurrence was 14 months and the range was 4 to 36 months. Of these patients, 9 eventually underwent additional interventions, namely, peripheral nerve block (4 patients), acupuncture and peripheral nerve block (3 patients), RF rhizotomy and peripheral nerve block (1 patient), and MVD (1 patient), and remainder only required dose adjustments. Two of nine patients who underwent additional interventions achieved an excellent outcome, three patients a good outcome, and four patients a final poor outcome.

Six patients (13.6%) experienced new ipsilateral facial numbness or paresthesia following GKS. Five of these showed transient sensory impairment, and the remaining one permanent deficits. Median time to an initial complaint of facial sensory impairment after GKS was 22 months with a range of 13 to 24 months. However, there were no complaints of other complications, such as, corneal reflex loss, anesthesia dolorosa or keratitis. The maximum dose, the distance from the center of target to pons, and the volume of the pons irradiated more than 18Gy were not associated with the complication rates with statistical significance (P=0.234, 0.495, and 0.305, respectively).

Discussion

Treatment of TN by GKS

GKS for TN has come to place a worthwhile treatment method²²⁾. In the present study, the overall treatment success rate (excellent, good or fair outcome) was 95.5% and the cure

rate (excellent outcome) was 50% after GKS (maximum dose 75~80Gy) for TN. Brisman²³ (maximum dose 75~76.8Gy) reported initial successful pain relief in 80% of patients, and Pollock, et al.^{15,16}, (maximum dose 70 and 90Gy) in 86 and 93% of patients, respectively. Massager, et al.¹¹, (maximum dose 90Gy) were successful in treating 94% of patients, Kondziolka, et al.⁷, (maximum dose 60~90Gy) in treating 85.6%, and Sheehan, et al.²⁰, (maximum dose 50~90Gy) in treating 70%. Although the results reported by different authors are fairly similar, details of the treatment techniques and analysis methods used, such as, maximum dose, target localization, the numbers of shots, the criteria used to quantify pain relief, numbers of patients, and the durations of follow up are diverse.

It is well known that higher radiation doses are necessary for a better treatment outcome after GKS for TN. Nicol, et al.¹³ who used 90Gy as a maximum radiation dose reported an excellent outcome in 73% of patients, and an excellent, good or fair outcome in 95% of patients, and thus, suggested that 90Gy represented an optimal maximum dose. However, higher radiation doses are accompanied by increased risks of adverse effects. Pollock, et al.¹⁶ compared patients irradiated with a maximum radiation dose of 80Gy with the patients irradiated at 90Gy, and reported that the latter group was associated with increased rates of trigeminal sensory disturbance with statistical significance. Similarly Brisman, et al.²³ reported that no benefit was gained from increasing the radiation dose beyond 70Gy, although the number of patients treated with a higher dose was limited. Nevertheless, although no randomized prospective study has been conducted to ascertain the optimal maximum radiation dose, a maximum dose between 70Gy and 80Gy is regarded as a reasonable by many authors^{16,19,24}. The treatment plan of the present series corresponded to these guidelines and the majority of patients (90.9%) received 80Gy as a maximum radiation dose and showed treatment outcomes that were comparable to those of previous studies.

Many GKS centers have debated optimal target localization for the treatment of TN. Many centers have preferred the root entry zone (REZ) of the trigeminal nerve as an optimal target^{7,13,16,19,24}. Regis, et al.¹⁸ used the plexus triangularis as a target, which is located far-anterior to the REZ. They reported an excellent outcome rate of 87% and a painful relapse rate of 10%. Despite the acceptability of these results, Massager, et al.¹¹ demonstrated that a far-anterior target was no better than the

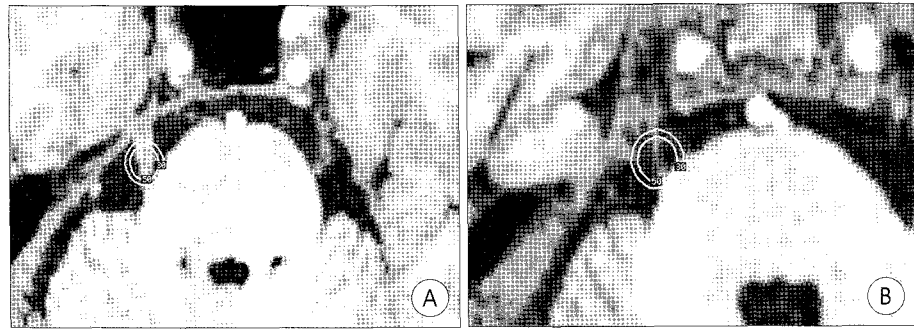


Fig. 3. Two axial T1-weighted three-dimensional spoiled gradient images depicting the differences in the anatomical characteristics, such as length, width, shape, and subsequently volume irradiated more than 40Gy. The inner circle represents the 50% isodose curve, and the outer circle the 30% isodose curve.

REZ and pointed out limitations of previous study indicating that no description of the post-GKS medication regimen was provided, no data from the follow-up period were available, and no statistical analysis was performed. These workers also recommended that the nerve should be targeted at a distance of 5 to 8mm from the brainstem to achieve both a higher pain relief rate and a lower complication rate. Alpert, et al.¹¹ have found that patients with two isocenter shots were more likely to receive a higher radiation dose and showed greater pain outcome improvements. They have concluded that an increased number of shots allow a higher radiation dose and that this is not associated with a higher complication rate or pain relapse rate with progressive dose escalation.

Anatomical considerations in GKS for TN

The fact that the maximum dose is related to the treatment outcome of GKS for TN has been well known. In this study, the volume of the nerve irradiated more than 40Gy was correlated with the treatment outcomes. These findings show that the anatomical and morphological variations can cause the discrepancies of the concentrated radiation dose to the constant nerve volume though the same maximal radiation dose was prescribed and those discrepancies subsequently can influence on the treatment outcomes. For instance the thin and long nerve makes a difference from the thick and short nerve in point of the volume of the nerve irradiated more than constant radiation dose, and subsequently the radiation dose to the constant nerve volume (Fig. 3). In the future, therefore, the study concerning the relationship of the anatomical characteristics of the trigeminal nerve and the treatment outcomes and the more delicate targeting techniques of GKS for TN should be planned.

Recurrence and complications of GKS for TN

The determination of latency to pain recurrence necessitates long-term follow-up to precisely evaluate GKS for TN treatment outcomes. Repeated GKS might be more appropriate

than peripheral nerve block to patients suffering recurrent pain, as previously reported^{3,4,14,22}.

The only noticeable side effect after GKS was of facial sensory impairment. In the present study, the mild or transient sensory impairment rate was 13.6%, and the problematic sensory impairment rate was only 2.2%. It is generally accepted that GKS has its merits, because it is a less invasive modality than MVD and other ablative interventions⁶. However, long-term follow-up and careful neurological examinations are required to evaluate delayed sensory impairment.

Conclusion

GKS remains an effective and reasonable alternative treatment modality for those unwilling or unable to undergo more invasive interventions for TN. Anatomical considerations during the planning of GKS may provide useful predictive information for the clinical outcome.

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Commentary

Of interest in this article is the potential relationship between the volume of the trigeminal nerve and outcome after radiosurgery. The authors state that there is a significant correlation between pain relief and the volume of trigeminal nerve irradiated more than 40Gy, but no relationship was found between complication/recurrence and nerve volume/dose. The result may be interpreted that prescribed dose need to be higher for thick trigeminal nerve. There are many literatures about factors that may influence the outcome after radiosurgery for trigeminal neuralgia, however, only a few factors such as dose and prior surgical treatment are accepted to have significant influence on outcome. A study similar to this article was performed by Regis et al². Though they used different target of irradiation they did not found statistically significant relationship between trigeminal nerve volume within 50% isodose line and outcome. Recently, it was reported that presence of neurovascular compression was related to better outcome¹. So current consensus is that adequate dose of irradiation in typical trigeminal neuralgia without prior surgical intervention produces the best results. Many other factors are not clearly detrimental or at most have only minor influence. I think that there is limitation to predict clinical outcome by anatomical factors because we don't know much about the pathophysiological or radiobiological difference accompanied by anatomical variation.

Also it seems that there are not many things to be improved in current radiosurgical techniques. However, tailoring of dose prescription according to anatomical characteristics deserves to be considered because even very minimal improvement of outcome is important for each patient.

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