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Abstract

Gamma knife surgery (GKS) is a minimally invasive treatment for brain diseases, and is currently used for functional disorders. Moreover, a revised version of Gamma knife system, “Model C-APS (automatic positioning system)” started to be installed in Japan since 2001. This latest model enables us to adjust coordinates by every 0.1 mm, and treat the patient automatically.

We have completed a retrospective study of 200 patients suffering from essential trigeminal neuralgia (TGN) treated with GKS in which the target was localized at the retro-gasserian portion of the nerve (We have treated 157 patients with essential TGN by “Model C-APS”). Among the patients, 106 could be followed up more than 6 months, and we evaluated a cause-and-effect relationship between the technical development and the clinical results. We categorized patients into three groups based on the term mentioned as follows; 1\textsuperscript{st} are the patients treated by Model B without completed fusion images (CFI) in between 1999 and 2001, 2\textsuperscript{nd} are the patients treated by Model B with CFI in 2002, and 3\textsuperscript{rd} are those treated by model C-APS with CFI since 2003. Clinical result, initial pain free was observed in 62.9\% (1st group), 85.7 \% (2nd group), 99.1\% (3rd group), complete recurrence was observed in 12\%, 8.3 \%, 0 \% for each groups, and postoperative complication was observed in 14.8\%, 14.3\%, and 9.5\% respectively. We believe that precise dose planning, so-called “Robotized Micoror Radiosurgery”, is...
the key to have a successful gamma knife surgery.

Key Words: Gamma knife, radiosurgery, trigeminal neuralgia, APS

Introduction

Gamma knife surgery (GKS) has become one of the most advanced neurosurgical treatments available. It is well known to be a minimally invasive surgical procedure that can control tumor growth, and moreover, it is efficacious and safe for control of functional disorders without craniotomy.

Recently, we have focused on the management of intractable pain, particularly trigeminal neuralgia (TGN) that has become a functional disease commonly treated by GKS worldwide. Many clinical reports have demonstrated that GKS can provide satisfactory results for patients without serious complications. In this chapter, we will present our institutional experience of GKS treatment for TGN.

Treatment options for TGN in general

In treating patients with TGN, we normally administer carbamazepine. When the effect is insufficient, we must consider surgical procedures such as glycerol rhizotomy, thermocoagulation, micro balloon compression, and microvascular decompression. The initial pain free rate is reportedly 74 to 94% and the recurrence rate 16 to 45% [1,2,3]. Recently, GKS has been regarded as an alternative treatment for TGN. For the elderly patients in whom surgery has failed and who suffer from possible risks associated with general anesthesia, GKS (the least invasive treatment) is particularly recommended.

Treatment Concept for TGN in GKS

In GKS for TGN, we normally use only 1 isocenter with a 4 mm collimator, and place it at the trigeminal nerve on the affected side. There are two different means of nerve target positioning. One target is exclusively the root entry zone (REZ), which is 2-4 mm from the emergence of the brain stem and the neuroanatomical border between oligodendrocytes and schwann cells. This strategy is favored by the Pittsburgh group. Another target is the retro gasserian region (RGR), which is located at the trigeminal incisula. This is the approach of the Marseille group. At our institute, we’ve employed the RGR method for two main reasons;

1) Efficacy and safety: The RGR target is adequately far from the brain stem for an optimal dose (90Gy at maximum) to the nerve. To date, we have achieved greater effectiveness while avoiding damage to the brain stem that could occur with high dose irradiation.

2) Efficacy and accuracy: we can correct the MRI distortion precisely
by using CT/MRI fusion images, because RGR targeting requires a bone landmark: the trigeminal incisula at the top of the petrous bone. On the contrary, it is impossible to directly correct MRI distortion with REZ targeting.

**Patient eligibility**

In the field of functional radiosurgery, appropriate patient selection is critical. TGN should be regarded as apparent TGN, to be confirmed clinically. Table 1 presents the features of six subjects with a tentative diagnosis of TGN. Before concluding that GKS can be done, all subjects must be fully informed. Our treatment aim is to prevent or reduce “electric discharge”.

**GKS procedure for TGN**

With frame fixation of the head, the frame must be placed parallel to the trigeminal nerve. Anatomical information regarding the nerve should also be confirmed. Next, we consider MRI sequence selection. Our aim is good visualization of the nerve in the cerebello-pontine cistern. Therefore, we normally use ultra-thin sliced (0.5mm) 3D heavily T2 WI and thin sliced (1.0mm) axial CT bone images. Before dose planning, we obtain MRI/CT fusion images. We use RGR targeting, and an irradiation dose of 90Gy, at maximum, considering the cerebello-pontine cistern space. If the cistern is narrow, however, we use a beam plugging technique to modify the 20% isodose line (18Gy area), making it parallel to the surface of the brain stem, thus avoiding excessive radiation of the brain stem. We assess the existence of MRI distortion using the MRI/CT fusion images and if any is detected, the amount of distortion is calculated precisely. After confirming the degree of distortion between CT and MRI images, we can correctly and precisely adjust it using an APS (automatic positioning system) by 0.1 mm level (Fig 1). The most important aspect of TGN is radiosurgery that delivers sufficient energy to the nerve with the smallest possible collimator. This means that the isocenter should fall precisely on the center of the true trigeminal nerve. We can achieve this precision by using 3D images (Fig 2) in the final stage of dose planning.

**Efficacy and Clinical Outcome**

We have treated one hundred and one patients with TGN (including two underwent second GKS) by gamma knife using RGR targeting. Among them, 147 followed up for more than 6 months were clinically evaluated. Initial pain reduction was observed in 98.6% (145/147), complete relief of “electric discharge” was observed in 91.1% (134/147). Delay of significant effects were ranged from 1 to 90 (mean 26.4) days. True recurrence was ob-
Fig. 1 demonstrates 2D image and Fig 3 shows 3D image. Both figures display the anatomical relationships including the trigeminal nerve and surrounding vital structures. The artery obviously conflicts the trigeminal nerve located on trigeminal incisula, and the never is properly covered by the 50% isodose area of 4mm isocenter.
served in 3.0% (4/134). Delayed recurrence was detected at 6-24 months (mean 9 months). Postoperative complications (hypoesthesia and dysesthesia) developed in 10.9% (16/147), but there were no mortalities. In those who received GKS only once, this rate was 9.5% (14/147). We also investigated clinical outcome according to the following treatment factors:

1) First generation group (1998-2001): treatment using model B without completely fusion images: 29 cases (27 cases with follow-up)
2) Second generation group (2002): treatment using model B with completely fusion images: 14 cases (all with follow-up)
3) Third generation group (2003-2004): treatment using model C-APS with completely fusion images: 157 cases (106 cases with follow-up)

Initial significant pain reduction was observed in 92.6% (25/27) of the first group, 100% of the second (14/14) and the third (106/106). The respective pain free (=complete relief of electric discharge) rate was 63% (17/27), 85.7% (12/14), and 99.1% (105/106). Those with true recurrence were 12% (3/25), 8.3% (1/12) and 0% (0/105). Postoperative complication rates were 14.8% (4/27), 14.3% (2/14) and 9.5% (10/105). Both third group cases that developed postoperative dysesthesia underwent GKS twice. Although the follow-up of the third group is yet insufficient, the results are clearly the best among the three.

At our institution, no significant predictive parameter has been identified from our clinical results, age, gender, affected side, topology, carbamazepine dose, delay of onset, previous intervention, cistern space, nerve atrophy, etc.

**Discussion**

**Optimal targeting**

TGN is the most common functional disease that can be controlled well by GKS. This has already been established as single isocenter irradiation with a 4mm collimator. However, clinical outcomes differ markedly from one institution to another.

Regis et al 3) (Marseille group) reported the clinical outcomes of 110 patients with RGR targeting in their prospective study. The initial pain free rate was observed in 97.2% (104/107), and delay of effects was seen at 26.2 days on average (1day-6months). True recurrence was observed in 14.4% (15/104), postoperative complications in 4.5% (5/107). On the other hand, Kondziolka et al 4) 5) (Pittsburgh group) reported their clinical experience with 220 patients in whom the initial pain free rate was 70.3%, that of true recurrence 13.6%, and postoperative complications were seen in 10.2%.

Fukuoka 6) evaluated treatment data (1145 cases) and clinical outcomes from multiple Japanese facilities and found that targeting position varies
among institutions. REZ targeting was more widely used in Japan (69.4%) than RGR targeting (20.4%). MRI/CT fusion images were not used in all institutions. Significant pain reduction was observed in 85% (973/1145) of cases, approximately 70% (800/1145) of whom had initial pain relief, and the delay of effect was 30 days on average (1-120 days). True recurrence was observed in 9.5% (109/1145), and delayed recurrence at 6.4 months on average (0-48 months). Postoperative complications developed in 12.3% (141/1145), including 1.4% (16/1145) with severe complaints. Clinical outcomes at our institution, particularly for the third group (model C-APS with MRI/CT fusion images) were close to those of the Marseille group.

So far, we have regarded RGR targeting as more advantageous than REZ targeting in terms of both efficacy and safety. The reasons are; 1) possible to irradiate with optimal dose (90Gy) with care to protect brain stem, 2) more accurate treatment with availability of MRI/CT fusion images.

**Indications for Elderly Patients with Intractable TGN**

In order to confirm GKS indications for elderly patients (more than 65 years old) suffering from intractable TGN, Hayashi et al. investigated 69 elderly subjects from the Marseille prospective study of 110 patients. Three issues were considered:

1) Comparison of clinical outcomes between elderly and younger groups: Initial pain relief was observed in 95.7% of the elderly group (vs. 100% in younger group), true recurrence in 16.7% (vs. 10.5% in younger group), and postoperative complications in 2.9% (vs. 5.4% in younger group). As to the response of TGN for GKS, the younger group had slightly more favorable results than the elderly group. However, results are apparently acceptable for elderly patients.

2) Comparison of clinical outcome in between previous surgical intervention (PSI) and no previous surgical intervention (NPSI) group: Initial pain relief was observed in 92.6% (PSI) and 97.6% (NPSI), true recurrence in 20% (PSI) and 24.4% (NPSI), and postoperative complications in 12% (PSI) and 9.8% (NPSI), respectively. The NPSI group had better results than the PSI group, indicating that elderly patients with TGN should undergo GKS as the critical procedure before surgical intervention.

3) Comparison of clinical outcomes between 90Gy and lower dose groups: Initial pain relief was observed in 96.8% of 90 Gy group (vs. 94.7% in lower dose group), true recurrence in 12.9% (vs. 27.8% in lower dose group), and postoperative complications in 3.2% (vs. 2.6% in lower dose group). Notably, the rate of true recurrence was significant higher in the lower dose group (p<0.05). On the other hand, the rate of postoperative complication did not differ significantly. Thus, 90 Gy appears to be an optimal dose for elderly patients.
In treating elderly patients with TGN, we recommend using the optimal radiosurgical dose (90Gy at maximum) before any surgical intervention.

**Overall Management and Treatment Indications for TGN**

If the patient is relatively younger, we recommend surgical intervention first, because the long-term effects of radiosurgery for TGN are yet unknown. Surgical procedures should be selected according to localization of the pain, severity of vessel involvement and patient choice (Fig.3). If surgical procedures fail or the effect is inadequate, we recommend GKS. If the patient is older, we recommend GKS as the first treatment for TGN prior to surgical procedures (Fig.3). Likewise, in young patients, if surgery fails or its effect is inadequate, we recommend a second GKS or other surgical procedures as necessitated by the patient’s condition.

**Conclusions**

Overall, 15,000 cases suffering from TGN have been treated by GKS worldwide. In addition, many published reports on clinical results and strategies have emphasized that GKS provides satisfactory results to most patients with few severe complications. To date, TGN has been widely accepted as an indication for GKS in the functional disease field. However, its mechanism of action has not yet been elucidated. If GKS produces destructive change in the nerve itself, patients will have sensory loss affecting half of the face.

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**Fig. 3: Clinical indication for essential Trigeminal Neuralgia.**

TGN: Trigeminal neuralgia, MS: Multiple sclerosis, MVD: Micro vascular decompression, RF: Radiofrequency.
Table 1. The list of treatment indications and diagnostic criteria for essential TGN

1) Electric Discharge
2) Unique Topography (no bilateral)
3) No neurological deficit (no sensory abnormality of face, no corneal hyporeflex)
4) No other type of pain (no atypical pain)
5) Trigger (touch & face washing/ tooth brushing/ mastication/ speech/ etc, swallowing)
6) Initial effect of Carbamazepine

A 90 Gy dose appears to be sufficient to produce a functional effect, termed the “Biological Differential Effect”, on the normal nerve/CNS without tissue ablation. This concept is expected to play an important role in treating other functional diseases. Epilepsy and cancer pain have been managed with pituitary radiosurgery. Therefore, both basic and clinical studies are needed to confirm the efficacy and safety of GK radiosurgery for functional diseases. Of course, it goes without saying that we need much longer follow-up after treatment to make an evaluation if GKS is an appropriate treatment for patients with TGN.

References