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Gamma Knife Radiosurgery for Trigeminal Neuralgia : Review and Update

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Accurate diagnosis of trigeminal neuralgia (TN) is the starting point for optimal treatment. Gamma knife radiosurgery (GKRS) is currently regarded as one of the first-line treatment options for medically refractory TN. GKRS is a less invasive treatment with a low risk of complications than other surgical procedures that provides a favorable pain control Barrow Neurological Institute (BNI) I-IIIb rate of >75% at short-term follow-up. Drawbacks of GKRS include the latency period before pain relief and higher recurrence rate compared with microvascular decompression. Therefore, repeat treatment is necessary if the initial GKRS was effective but followed by recurrence. The concept of dose rate and the biologically effective dose of radiation has been actively studied in radiation oncology and is also applied in GKRS for TN to achieve high safety and efficacy by prescribing the optimal dose. Recent progress in functional imaging, such as diffusion tensor imaging, enables us to understand the pathophysiology of TN and predict the clinical outcome after GKRS. Here, we review TN, GKRS, and recent updates, especially in the concepts of radiation dose, diffusion tensor imaging studies, and repeat treatment in GKRS for TN.

Key Words : Radiosurgery · Trigeminal neuralgia · Radiation dosage · Diffusion tensor imaging · Retreatment.

INTRODUCTION

Facial pain can be caused by various types of neurological disorders and the differential diagnosis is mainly based on the patient's description of symptoms. To achieve successful treatment outcomes in trigeminal neuralgia (TN) by determining the optimal treatment option, accurate diagnosis is key. In the International Classification of Headache Disorders, third edition, TN is defined as "a disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli." TN is classified into classical, secondary, and idiopathic TN. Classical TN is diagnosed when no cause other than neurovascular compression is apparent. Secondary TN is caused by underlying diseases such as multiple sclerosis, brain tumors, and vascular malformation. If magnetic resonance imaging (MRI) and electrophysiological tests show no significant abnormalities, the condition is considered idiopathic TN. A characteristic feature of TN may manifest with persistent background facial pain, which is referred to as TN with concomitant continuous pain. Previously, the terminology "atypical" or "type 2" has been used for this type of TN[68]. We have offered surgery (microvascular decompression, MVD), radio-

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surgery, and percutaneous procedures (radiofrequency thermocoagulation, balloon compression, and glycerol rhizotomy) to patients with medically refractory TN[66]. Indications, clinical outcomes, complications, and prognosis of each treatment option have been extensively studied and reviewed.

Gamma knife radiosurgery (GKRS) is currently regarded as one of the first-line treatment options for medically refractory TN since Lars Leksell used it for intractable TN patients in 1951[36]. GKRS shows a short-term (less than 1 year) pain relief rate (with or without medication) of higher than 75% and long-term efficacy of approximately 50–60% after 5 years and 30–40% after 10 years[33,40,41,52,65]. However, the recurrence rate is higher than 20% as demonstrated in multiple studies[43,63]. At a certain point in the clinical pathway, recurrence or treatment failure should be considered, and other treatment options such as repeat GKRS should be considered. And multiple studies on biologically effective dose (BED) have been conducted in the field of radiation oncology over the past 30 years. Functional imaging, including diffusion tensor imaging (DTI), has been applied in various neurological disorders. These approaches were also applied in the patients with TN after GKRS. Herein, we review GKRS for intractable classical or idiopathic TN, focusing on the recently described application of dose rate, BED, and DTI and the clinical outcome and feasibility of repeat GKRS.

PAST CONTROVERSIES ABOUT GKRS FOR TN AND CURRENT CONSENSUS

There were many controversial issues about the optimal conditions of GKRS in the early days of GKRS for TN. With the accumulation of clinical data, these issues have been clarified, although there are still some questions with no consensus. The optimal dose, target location, number of isocenters, and influence of dose rate were well defined in the early days of GKRS. In a trial by Lindquist et al.[37] in 1991, radiation was focused on the gasserian ganglion of the trigeminal nerve and was moved posteriorly to the retrogasserian ganglion and root entry zone (REZ)[33,51-53]. A higher rate of pain reduction was reported with a higher dose focused on the retrogasserian target, which is the distal part of the cisternal segment of the trigeminal nerve. However, sensory complications occurred more frequently the closer the target was to the brainstem. Although the results of the following clinical studies were not always consistent with the original report, a systemic review concluded that a higher dose on the retrogasserian target would be associated with more effective pain control and less frequent sensory complications compared to other targets[42,47,64,67]. A maximum dose of 70–90 Gy has been recommended based on outcomes from multiple retrospective analyses. In general, a higher dose is associated with more prompt pain reduction and a higher rate of overall response[29,31,32,39,52-54]. At the same time, a higher dose, particularly applied to the brainstem, is associated with a higher rate of trigeminal neuropathy[4,8,10,15,19,20,22,23,30,45,48,49,56]. Not only the absolute dose but also dose rate was suggested as a factor that might influence the outcome. The hypothesis was that a higher dose rate would result in a stronger biological effect if the absolute dose was the same[3,5]. Recent advances in knowledge related to this issue will be discussed in detail in the following part of this review. When GKRS using a single isocenter was compared with that using two isocenters, no benefit of using multiple isocenters was identified in prospective as well as retrospective studies[2,17,50]. Various prognostic factors were investigated. Typical pain features of TN, old age, definite vascular compression on MRI, and no history of surgical treatments were associated with better outcomes after GKRS[10,16,39,41,55]. Sensory changes after GKRS were associated with better pain relief, similar to other percutaneous procedures[14,18].

Currently, GKRS is one of the primary treatment options for TN and salvage treatment after the failure of other procedures. Although there is no high-level prospective randomized controlled trial or comparative study between GKRS and other modalities, distinctive features and current roles of GKRS can be summarized in the general context of clinical practice to support decision making. First, GKRS is the least invasive approach among the various treatment modalities except for medication. Procedure-related risks (e.g., hemorrhage, infection, cerebrospinal fluid leakage, nerve injury, etc.) are lower than in any other surgical procedure. Second, the outcome of GKRS is relatively unaffected by the neurosurgeon or individual patient characteristics. Experience or skill of the neurosurgeon or characteristics of the patient, such as anatomical variations, have less influence on the outcome of GKRS than on the outcome of MVD or percutaneous procedures. Third, GKRS is the only treatment modality that is accompanied by a latency period before pain relief[33]. Fourth,

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sensory complications after GKRS are lower than in various percutaneous procedures[6,38,64]. Fifth, initial pain relief and freedom from recurrence are not superior to MVD performed by experienced neurosurgeons[38]. Sixth, durability of the effectiveness of GKRS is superior to medication or other percutaneous procedures. Finally, the outcome of GKRS is not yet fully predictable, and further studies need to elucidate these hypothesis and questions to make GKRS a better treatment modality in TN.

DOSE RATE AND BIOLOGICALLY EFFECTIVE DOSE IN GKRS FOR TN

Cobalt-60, the radiation source of the GKRS, has a half-life of 5.26 years and decays spontaneously. The dose rate, which is defined as the amount of radiation absorbed by tissues per unit time, is reduced by half and the treatment duration is doubled after passage of a half-life when the prescription dose is constant. In radiation oncology, lower dose rates allow for more efficient repair of accumulated sublethal DNA damage within both tumors and surrounding normal tissues, which could potentially impact both tumor control and risks for toxicity in later phases of the treatment. Similarly, the dose rate of cobalt-60 was hypothesized to affect pain control in patients with TN[57]. Calibration dose rate (CDR), a physical measurement in a standard phantom, is not the same as the dose rate in the tissue of a human patient. Because patient parameters depend on the activity of the sources, the collimator used, the individual patient geometry, and the degree of sector blocking, BED of a given physical radiation dose in tissue will decline as a function of increasing exposure time[63].

Few studies have evaluated the impact of CDR or BED on clinical outcomes in TN, and the results were inconsistent. Balamucki et al.[5] studied 239 GKRS procedures in patients with TN and found no significant association between dose rate or treatment time and pain control rate. Arai et al.[3] studied 165 patients with medically intractable TN who underwent 80-Gy GKRS using a single 4-mm collimator uniformly. The authors divided the patients into a low dose rate (1.21 to 2.05 Gy/min) and a high dose rate (2.06 to 3.74 Gy/min) group. The results were not significantly different in terms of pain control or trigeminal dysfunction[3]. Both studies claimed that the patients could consider receiving similar treatment with GKRS at any time during the first half-life of a cobalt source. However, recent studies have shown opposite results. Lee et al.[35] suggested that a higher dose rate of >2 Gy/min results in more pain control at early follow-up and a lower recurrence rate at later follow-up. The authors studied 133 patients with TN who were treated with 80-Gy GKRS using a single 4-mm isocenter without blocking, and within a dose rate from 1.28–2.95 Gy/min[35]. Tuleasca et al.[63] suggested that safety and efficacy of GKRS in patients with TN might be achieved by prescribing a specific BED. Specifically, they calculated an optimal BED range associated with both long-term pain-free incidence of 90% and low risk of hypesthesia development of less than 10%. The optimal BED was determined to be 1820–1962.5 $Gy_{2.47}$ (the BED was calculated with the tissue specific constant of 2.47. The tissue was white matter of central nervous system, and the authors named the unit of BED value of GKRS for TN as $Gy_{2.47}$)[63]. A recently published paper by Barzaghi et al.[7] also shows that the radiation time and the prescription dose are important factors using the concept of BED in terms of long-term pain control. Long-lasting pain control was observed with a value of 2.5 Gy/min[7]. However, the number of participants in this study was very small, and earlier studies showed negative results. Further studies will need to elucidate the correlation of dose rate and outcomes and its clinical significance.

DTI IN TN

DTI can identify brain white matter tracts by tractography and offers a non-invasive, *in vivo* approach to assess axon and myelin microstructures using quantitative diffusion parameters. Fractional anisotropy (FA) is the most commonly used DTI metric to characterize white matter microstructure and is a strong prognostic indicator of clinical progression and treatment response in several pathological disorders. Other DTI metrics include radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD), which correlate with myelination, axonal integrity, and neuroinflammation, respectively[1,44,58-60,62]. Recent multisensor, high-spatial-resolution nerve-specific DTI protocols have enabled detailed visualization of both the peripheral and central (brainstem) components of the trigeminal nerve pathway[9,11,12].

TN studies using DTI have been performed to understand

the pathophysiology and to show the clinical correlation of DTI. Patients with TN have lower FA and higher AD, RD, and MD within the TN-affected, ipsilateral trigeminal nerve REZ[13,24,34]. Trigeminal tractography could detect the radiosurgical target where FA values were dropped by 47% focally. This finding showed highly focal changes after GKRS. Radial but not axial diffusivities increased significantly after GKRS, suggesting that this irradiation technique primarily affects myelin. The reversal of FA towards baseline values correlated with pain recurrence at the long-term follow-up[25]. Different patterns of pre-treatment diffusivities can differentiate responders from non-responders to treatment. Long-term responders have unique microstructural abnormalities (lower AD and MD) localized to the cisternal segment of the trigeminal nerve, whereas non-responders have abnormalities located more centrally (lower FA at REZ, higher AD at the pontine segment). This may reflect that the TN-induced structural alterations may have functional consequences, resulting in central manifestations of TN pain[27]. FA remained lower at the long-term follow-up (24 months after GKRS) in responders. Therefore, a decrease in FA was suggested to be potentially useful as a biomarker for successful pain relief[28].

In a recently published paper, different DTI metrics were found across different subtypes of TN (classical, multiple sclerosis, solitary pontine lesion) that could differentiate good treatment responders and classical TN from other subtypes. This clinical response spectrum was associated with the degree of brainstem trigeminal fiber microstructural abnormalities. Specifically, microstructural abnormalities in the affected pontine trigeminal fibers (lower FA and higher RD) were found in treatment non-responders compared with responders and controls[62]. Further studies are needed to strengthen the role of the DTI metrics as biomarkers in TN. These biomarkers may be used in the differential diagnosis of TN, which relies solely on the patient's description and in predicting the prognosis after treatment.

REPEAT GKRS FOR TN

Patient characteristics important for determining the optimal treatment option usually do not change when TN relapses. If there is evidence of neurovascular compression and the general condition of the patient allows, MVD is considered as the first treatment option. However, if the patient is inoperable and repeat GKRS is considered as the next treatment option, the efficacy and complications are key factors in choosing repeat GKRS. Repeat GKRS shows favorable clinical outcomes (BNI I–IIIb) in a median of 71.5% (range, 50–95%) of the patients. Although only minimal facial numbness was reported by patients, the occurrence of trigeminal nerve dysfunction was increased following repeat GKRS in a median of 42% (range, 11–74%) of the patients. The maximum target dose was reduced at the second radiation in most institutions by a median of 10 Gy (range, 0.9–35)[4,8,10,15,19,20,22,23,30,45,48,49,56]. The trigeminal target at the second GKRS was usually placed more distally or proximally to minimize overlap. Tempel et al.[61] placed the target where the overlap of the two radiosurgical volumes was by approximately 50%.

Several studies have tried to identify prognostic factors for repeat GKRS in patients with recurrent TN. Age, gender, duration of symptoms prior to initial GKRS, and the interval between GKRSs have no significant effect on outcomes[45]. Good outcome (BNI I–IIIb) following the first GKRS is a major predictive factor for favorable response to repeat GKRS[22,23,45,46,48]. Thirty-nine percent of patients with no response to the first procedure could still be treated by repeat GKRS[46]. The facial numbness following not only repeat GKRS but also initial successful GKRS is another well-known positive predictive factor for a good response to repeat GKRS[4,22,26,30,48]. However, a higher cumulative GKRS dose was associated with a greater likelihood of sensory sequelae, and the cumulative doses to the lateral pontine edge (>44–108.5 Gy) or to the target (115–130 Gy) were correlated with a newly occurring trigeminal sensory loss[4,15,26,46]. Most of trigeminal nerve dysfunction was minimal facial numbness after repeat GKRS; the most significant form was anesthesia dolorosa, which occurred in 1.3% of the patients from one study[22].

An additional third GKRS for recurrent TN after repeat GKRS has not been well described. The few reports have been limited to case reports or case series with a small number of patients. Tempel et al.[61] performed a third GKRS in 17 patients, with a favorable pain control rate (BNI I–IIIb) in 94% of the patients initially and 76.4% at a mean follow-up of 22.9 months (range, 3–60). The outcome of the third GKRS was comparable to the outcome of the second GKRS for TN. The maximal treatment dose at the third procedure was a mean of 62.9 Gy (range, 40–80), and the mean cumulative dose was

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208.5 Gy (range, 150–240). Although three patients (17.6%) developed new or had worse trigeminal nerve dysfunction after the first GKRS and another two patients (11.8%) after the second procedure, no patient experienced additional sensory disturbances after the third procedure[61]. A recently published study enrolled 22 cases, and favorable pain control rate (BNI I–IIIb) was achieved in 81.8% of these cases. The 1, 3, and 5-year rates of favorable pain relief were 62.7%, 53.8%, and 40.3%, respectively. The median dose at the third GKRS was 75 Gy (interquartile range, 75–80), and the median maximal radiosurgical dose to the trigeminal nerve was 222.4 Gy (interquartile range, 200.8–232.3). Ten cases (45.5%) experienced new or worsening facial numbness, a rate similar to that of the second GKRS. Four cases of dry eye and one case of corneal abrasion were reported, especially in cases with proximally placed shots[21]. Third GKRS procedure for TN may be a viable treatment option in patients who are inoperable. Treatment results are similar to those seen in the initial and second GKRS, but trigeminal nerve dysfunction occurs at a higher rate if the shot is placed proximally along the nerve[21,46].

CONCLUSIONS

GKRS has become one of the well-established primary treatment modalities for medically refractory TN and salvage treatment for patients following the failure of other treatments. It is the least invasive treatment option, with the highest safety profile among various neurosurgical treatment modalities. Initial pain relief can be achieved in the majority of patients, and durability of the effectiveness is favorable compared to other treatments including medication. Meanwhile, disadvantages of GKRS include a latency period before pain relief and a substantial rate of recurrence at the long-term follow-up. Recent advances in radiation biology and neuroimaging are expected to refine GKRS techniques and improve outcomes in patients with TN.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : JIL; Writing - original draft : SL; Writing - review & editing : SL, JIL

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