Effect of radiation dose on the outcomes of gamma knife treatment for trigeminal neuralgia: A multi-factor analysis

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Abstract

**Aim:** To analyze the effect of different radiation variables on the outcomes of treatment for trigeminal neuralgia (TN). **Materials and Methods:** Seventy-three patients with refractory TN were treated with a maximum dose of 75-90 Gy using either one (n = 41) or two (n = 32) isocenters and were intensively followed up. The integrated dose delivered to the trigeminal nerve root within the prepontine cistern and the nerve root volume was calculated using the Gamma-Plan system. Relationships between the clinical outcomes and radiation variables were statistically analyzed using a combination of Fisher’s exact test and multivariate analyses. **Results:** At their last follow up, 21 patients (28.8%), 22 patients (30.1%), 19 patients (26%), 6 patients (8.2%), and 5 patients (6.8%) had Grade I-V pain outcomes, respectively, and the average mean dose delivered to the trigeminal nerve root, average integrated dose (mJ) and nerve root volume in prepontine cistern were 45.29 Gy, 4,26 mJ, and 98.47 mm$^3$, respectively. The pain relief rate was not significantly improved by a higher amount of integrated dose received by the trigeminal nerve root in prepontine cistern, however, incidence of trigeminal nerve toxicity was increased ($P = 0.005$). **Conclusions:** Our limited results suggested that a higher integrated dose might increase the incidence of trigeminal nerve toxicity with no significant benefits in pain relief when the maximal doses were within 75-90 Gy. The protocol for increasing radiation variables such as longer nerve exposure length and higher maximal dose is not recommended as a routine approach and more randomized studies with large number of cases would be required to verify the best treatment strategy of gamma knife radiosurgery for TN.

Key words: Dose-volume histogram, gamma knife, pain control rate, radiosurgery, radiation dose, trigeminal neuralgia

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Introduction

Although gamma knife radiosurgery (GKR) represents an effective treatment option for trigeminal neuralgia,[1-4] there is a lack of consensus on the best-suited treatment protocol. Radiation variables are crucial factors of the treatment protocol and can significantly affect its outcome. These variables include an ideal isocenter location, optimum irradiated nerve length, treatment volume, and maximal radiation dosage. Historically, the aim of GKR treatment for TN is to gain the best pain relief with minimal and acceptable morbidity. Though a close relationship between among the efficacy, different occurrence rate of complication, and maximal radiation dose has been reported by several studies with heterogeneous treatment philosophies,[2,5-8] the effect of radiation dose for the entire length of the trigeminal nerve root on pain relief and further complications is not clear. The goal of this single-institution retrospective
series was to present a dose–volume data set that may help to achieve a better understanding of radiobiological effect on clinical outcomes following GKR for TN.

Materials and Methods

Patients
Eighty patients with idiopathic TN who were medically refractory or experiencing intolerable side effects underwent GKR from July 2010 to May 2013 at our hospital. Prior to the treatment, routine magnetic resonance imaging (MRI) ruled out symptomatic TN caused by tumors, infarction, or multiple sclerosis. Seventy-three patients (90.1%) were followed up with a median time of 12 months (range: 6-37 months). The average age was 63.5 years (range: 37-87 years) and thirty patients were male. The most common area of pain was in the V1, V2, and V3 nerve distributions (31.1%). Twenty-one patients (26.3%) had undergone previous surgical procedures, including percutaneous rhizotomy (glycerol or radiofrequency ablation), GKR, and microvascular decompression. Before GKR treatment, patients had experienced the symptoms for a mean duration of 7.3 years (range: 0.25-20 years) and facial numbness had been reported by six patients. The clinical characteristics of patients are detailed in Table 1.

Gamma-knife radiosurgery
A Leksell stereotactic multifunctional frame (Elekta Instruments, Sweden) was attached to the patients’ head, parallel to the trigeminal nerve root, under local infiltration anesthesia in a standard manner. Using the sequences of turbo spin echo and constructive interference in steady state sequences, MRI images were fused for preoperative localization by the image fusion function of GammaPlan version 9.0 (Elekta Instruments). The maximum central doses of 75-90 Gy were delivered to the patients with single isocenter (56.2%) or double isocenters (43.8%) in 4 mm. The target of the treatment was the trigeminal nerve root entry zone (REZ). All patients underwent treatments using Leksell Gamma Knife model C (Elekta Instruments, Stockholm, Sweden). Plug pattern was used to limit the doses to the pons if necessary [Figure 1].

Outcome assessment and analysis
Regular follow-up visits were suggested at 3, 6, 12 months, and annually thereafter following GKR. Telephonic or personal interview were used to obtain follow-up information, including the time to the onset of pain relief, the degree of pain relief, and treatment complications by two medical residents who were “blind” to the patients’ medical history. Based on the Barrow Neurological Institute (BNI) score for TN,[1] we classified pain relief after treatment into five grades: Grade I = no pain without medication, Grade II = occasional pain not requiring medication, Grade III = some pain adequately controlled by medication, Grade IV = some pain not adequately controlled by medication, and Grade V = severe pain with no pain relief. We defined Grade IV and Grade V as treatment failure. Using the dose–volume histogram module of GammaPlan, we retrospectively calculated the mean and integrated dose delivered to the trigeminal nerve root within the prepontine cistern and the nerve root volume, respectively [Figure 2]. The relationships between pain relief outcome, trigeminal nerve dysfunction, different dosimetric variables, age of patients, and previous neurosurgical procedure for TN were further analyzed.

Statistical analysis was performed with the Statistical Package for the Social Sciences software (version 14.0;
SPSS, Chicago, IL, USA). Fisher’s exact test was used for nominal data. Multivariate analysis was performed to determine the significance of radiation variables factors to pain relief and complication by using stepwise logistic regression. Statistical significance was set at a P value of ≤ 0.05.

Results

Radiation dosimetry

Depending on the GammaPlan treatment planning system, we calculated several dosimetric variables, which are summarized in Table 2. The average mean dose delivered to the trigeminal nerve root, average integrated dose (mJ) and nerve root volume in prepontine cistern were 45.29 Gy, 4.26 mJ, and 98.47 mm$^3$, respectively. By using multiple linear regression, we found that the mean dose ($P < 0.001$), nerve root volume in prepontine cistern ($P < 0.001$), and number of shots ($P < 0.001$) were significantly related to the integrated dose (mJ).

Pain relief

At their last follow-ups, 21 patients (28.8%), 22 patients (30.1%), 19 patients (26%), 6 patients (8.2%), and 5 patients (6.8%) had GRADE I-V pain outcomes respectively. Sixty-two out of 73 patients (84.9%) reported an improvement in pain after GKR. We did not observe a significant relationship between integrated dosage (mJ) and pain relief using logistic regression. The results of multiple logistic regression revealed that the center dose, number of isocenters, nerve root volume in prepontine cistern, age of patients, sex, and previous neurosurgical procedure for TN did not affect treatment efficacy significantly as summarized in Table 3. However, the development of post-treatment trigeminal nerve dysfunction and pain side was significant impact factors for improving treatment efficacy. The median time to onset of pain relief was 1 month after radiosurgery (range: immediately to 18 months). The difference in latency was not significantly related to the prescribed and integrated doses delivered to the volume of the trigeminal nerve root within the prepontine cistern. Recurrence was observed in 9 of 62 (14.52%) responding patients at a median time of 18 months (range: 2-42 months) after pain relief. Of these 9 patients, 3 had Grade I relief and 6 had Grade III relief initially.

Toxicity

Newly developed or increased trigeminal nerve dysfunction (numbness or paresthesia) were observed in 29 patients (39.7%), none of which experienced dysgeusia, dry eye syndrome, or anesthesia dolorosa after GKR. The trigeminal dysfunction was persistent during follow up and within patients that reported trigeminal nerve dysfunction; 11/29 (37.91%), 12/29 (41.38%), 5/29 (17.27%), and 1/29 (3.45%) achieved Grade I, II, III, and IV pain relief, respectively, with none of the patients experiencing Grade V pain relief. We observed a significant trend for increased incidence of trigeminal dysfunction when higher integrated doses were administered to the trigeminal nerve root within the prepontine cistern by univariate analyses ($P = 0.005$), despite the small number of cases. A significant difference was also found in trigeminal nerve toxicity incidence between two-isocenters and one-isocenter ($P = 0.003$).

Table 2: Follow-up data for different dosimetric variables, nerve dysfunction and pain control

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Grade V</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN in prepontine cistern</td>
<td>21 (28.8%)</td>
<td>22 (30.1%)</td>
<td>19 (26%)</td>
<td>6 (8.2%)</td>
<td>5 (6.8%)</td>
</tr>
<tr>
<td>Avg. mean dose (Gy)</td>
<td>45.27</td>
<td>46.63</td>
<td>44.17</td>
<td>48.27</td>
<td>40.22</td>
</tr>
<tr>
<td>Avg. integrated dose (mJ)</td>
<td>4.33</td>
<td>4.47</td>
<td>3.99</td>
<td>4.28</td>
<td>4.12</td>
</tr>
<tr>
<td>Avg. volume (mm$^3$)</td>
<td>93.88</td>
<td>101.34</td>
<td>100.55</td>
<td>89.77</td>
<td>107.1</td>
</tr>
<tr>
<td>Avg. maximum dose (Gy)</td>
<td>87.2</td>
<td>86</td>
<td>84.4</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>One isocenter: two isocenters</td>
<td>1.625</td>
<td>1</td>
<td>1.375</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>TN dysfunction</td>
<td>11 (52.38%)</td>
<td>12 (54.55%)</td>
<td>5 (26.32%)</td>
<td>1 (16.67%)</td>
<td>0</td>
</tr>
<tr>
<td>Recurrence of pain</td>
<td>3 (14.29%)</td>
<td>0</td>
<td>6 (31.58%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean time to pain relief (M)</td>
<td>1.46</td>
<td>2.96</td>
<td>1.5</td>
<td>1.09</td>
<td>NA</td>
</tr>
</tbody>
</table>

Avg. - Average, TN - Trigeminal nerve, NA - Not applicable
The results of this study suggested that the pain relief rate was not significantly improved by a higher amount of integrated dose received by the trigeminal nerve root in prepontine cistern; on the contrary, increasing the incidence of trigeminal nerve toxicity. Integrated dose is influenced by many factors, such as the mean dose, maximal dose, trigeminal nerve root volume in the prepontine cistern, and number of shots or nerve length irradiated in this study.

Kondziolka et al.[9] found that greater than 70 Gy should be prescribed for trigeminal neuralgia radiosurgery. Subsequently, Regis et al.[10] alleged that maximal dose of more than 90 Gy would increase the incidence of facial sensory loss and paresthesia. Therefore, it is generally accepted that the maximal radiation doses in treatment of TN should be prescribed between 70 and 90 Gy. As a traditional method, studies of GKR for TN are usually described by the maximal dose, which may be the most important factor of the treatment protocol. However, the results of our study and that of aforementioned studies[4,8,11] suggest that the pain relief rate and trigeminal nerve dysfunction were related not only to the maximal dose but also to many other factors, for example, cumulative dose. Dvorak et al.[12] reported that cumulative dose more than 130 Gy was more likely to result in successful pain control, but was also more likely to develop new neural dysfunction. While Huang et al.[13] indicated that cumulative doses above 115 Gy were found to be associated with non-facial numbness and facial numbness. Radiosurgery as a destructive technique itself correlates pain relief outcome after radiosurgery and trigeminal nerve injury together. Although the patients treated with higher dose might experience a higher rate of pain relief after GKR treatment[14] (but this increase is not in accordance with increased incidences of complications), simply increasing the prescript dose without limit might also increase the incidence and severity of postoperative complications beyond a patient’s tolerance capacity.[8,14,15] Though we and others did not observe a statistical significance when considering the role of an integrated dose or maximal doses for evaluating the pain relief rate within a therapeutic window of 75-97 Gy for TN albeit with higher complication rates,[4,8,11] we may use a relatively lower prescribed dose, higher than 70 Gy,[9] to prevent increased toxicity rates. In addition, we supposed that an integrated dose to the trigeminal nerve root might provide useful information to understand better the radiobiological effects on clinical outcomes following GKR for TN.

Our study as well as other studies use the root entry zone within the trigeminal nerve as the most suitable target, since this region is the transition point from Schwann cells to oligodendrocytes and may provide a difference in radiosensitivity along the nerve.[9] Alternatively, Régis et al. pointed out that a high-dose irradiation of the proximal nerve root could potentially endanger it and suggested an anterior targeting method as an alternative to avoid complications with superior pain control.[14] While compared to REZ, the distal targeting method studies did not significantly reduce the rate of complications.[17,19] These series imply the lesion of the trigeminal nerve in prepontine cistern is more important than proximal/distal isocenter location while considering complication rates.

Radiation exposure length of the trigeminal nerve (number of shots) was directly related to the radiosurgery treatment volume and integrated dose for the trigeminal nerve root. Our results (higher rate of trigeminal dysfunction without significantly increased pain relief rate) were similar to some of previous studies that increased irradiation length of the nerve.[2,4,5,20] Analogously, based on the results of Marshall K’s study,[8] patients with shorter length of trigeminal nerve in prepontine cistern could have better outcomes during follow up. Interestingly, one study reported that greater brainstem exposure volumes and lower trigeminal nerve treatment volume might result in improved pain relief without a significant difference in trigeminal nerve toxicity.[21] This study implies that the distance between isocenter and the brainstem may affect treatment outcome. Conversely, in our study, the trigeminal nerve treatment volume irradiated in the prepontine cistern did not directly influence the pain outcome and complication. To the best of our knowledge, there is an inverse relationship between brainstem exposure volumes and trigeminal nerve treatment volume. This is because the increasing diameter and length of the nerve lend credence to farther and larger anatomical targets and a higher
prescription dose along the nerve (concerned that radiation dose received by the brainstem being too high to tolerate). Therefore, the trigeminal nerve volume in the preoptic cistern, though not equal to treatment volume, has an individualized anatomical factor and may indirectly influence the outcome of treatment.

In the present study, initial treatment history was not a factor that affected pain control or complication, consistent with previously published reports,[17,22,23] while contradicting other analyses.[1,24‑26] This may be caused by the heterogeneous duration of symptoms, side and distribution of pain, treatment factors, presence of preoperative facial anesthesia, and treatment philosophies. Secondly, we may make prior invasive treatment a gross over simplification. Little, A. S et al. suggested that unlike other invasive procedures, the strongest predictor of GKrSR failure was a history of prior MVD.[27] This implies prior invasive treatments may be different from each other than we think and these treatments cannot be analyzed as a single factor. In addition, the type of pain that patients suffered from in our study was not identical. Atypical features or typical pain type may influence our data analyses differently. Of note, this is not the end-point of observation for most of the patients and a longer follow-up period is necessary to fully assess the incidence of late complication and recurrence.[28] Hence, the results of patients in the present series are self-limiting and a continuous follow-up is yet to be carried out. Our results suggest that there may be a threshold of an integrated dose in the treatment of TN with GKrSR, which can provide promising treatment outcomes with a lower risk of complication and recurrence.

References


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