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Repeat gamma knife radiosurgery for recurrent or refractory trigeminal neuralgia

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Background: Repeat gamma knife radiosurgery (GKRS) is considered to be an effective treatment for refractory or recurrent trigeminal neuralgia (TN). **Aims:** The purpose of this report was to demonstrate the relationship between the outcome of repeat GKRS and prior operative procedures on patients with recurrent or refractory TN. **Materials and Methods:** A retrospective analysis was performed on 34 patients with refractory or recurrent TN who had undergone repeat GKRS; 21 patients had undergone other types of procedures, 11 of whom had undergone more than three such procedures prior to radiosurgery. The maximum dose of the repeat procedure was between 60 and 75 Gy. The mean follow-up time was 21.6 months. **Statistical Analysis Used:** The log-rank test and Fisher's exact test were used to analyze the data. **Results:** Excellent pain relief was achieved in 14 patients (41.2%) after repeat GKRS, while a successful outcome occurred in 29 of 34 patients (85.3%). Better pain relief occurred in the patients who did not have a prior procedure or who had undergone fewer than three prior procedures (P = 0.042). Twenty-four of 25 patients (96.0%) who had recurrent pain had a successful operation and five of nine patients (55.6%) who did not have significant relief of pain after the first procedure had a successful operation. The difference was statistically significant (P < 0.01). Only four patients had mild complications. **Conclusion:** It is more likely to relieve pain in patients with recurrent or refractory TN who did not have a prior procedure or who had fewer than three procedures before undergoing their first GKRS. Moreover, it seems that patients who had a good response following the initial GKRS had better results after a repeat procedure.

Key words: Gamma knife surgery, pain, radiosurgery, trigeminal neuralgia

Since Leksell[1] performed gamma knife radiosurgery (GKRS) on 63 patients with trigeminal neuralgia (TN), GKRS is considered to be an effective therapy and a minimally invasive surgical approach for medically or surgically intractable TN, especially for the patient who has failed other surgical procedures.[2-8] Although the reports[3,9-15] show that there is a high rate of pain relief (77-95%) after the first GKRS, there is a definite percentage of patients who require repeat GKRS and who experience persistent or recurrent pain after the first procedure. In this paper, we retrospectively analyzed the clinical data of 34 patients who underwent repeat GKRS with persistent, particularly severe, medically or surgically refractory or recurrent TN. We divided the patient cohort according to whether they had previously undergone other operative procedures before radiosurgery to ascertain the treatment effect.

Materials and Methods

Patient population

Between June 1999 and December 2005, a total of 322 patients with medically unresponsive TN underwent GKRS at the Tangdu Hospital of the Fourth Military Medical University and the First Hospital of Xi'an Jiaotong University. Thirty-eight patients required further intervention for delayed, recurrent symptoms or inadequate pain relief and 34 patients accepted repeat GKRS, all of whom had failed medical management before GKRS. Of these patients, 21 (61.8%) had undergone previous surgical interventions and 11 patients (32.3%) had undergone more than three procedures. The remaining 13 patients selected GKRS as their first and second surgical procedures. Two patients (5.9%) had previously been diagnosed with multiple sclerosis (MS). We excluded patients who achieved good pain relief by microvascular decompression (MVD) after initial GKRS. Tumor-related TN was excluded from this analysis.

The patient characteristics are summarized in Table 1. The male to female ratio was 14:20. The median age at the time of the first GKRS of the retreated patients was

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Table 1: Patient characteristics

Characteristics	Number
Age at first GKRS (median range years)	68 (42-87)
First onset age (median range years)	55 (36-71)
Male/female	14/20
Right/left	22/12
Pain duration prior to initial GKRS (median range months)	63 (5-169)
Interval between initial and repeat GKRS (mean range months)	17.4 (8-34)
Follow-up time after repeat GKRS (mean range months)	21.6 (7-41)
Number of procedures prior to GKRS	
0	13
1-2	10
>3	11
Multiple sclerosis	2
Recurrent/refractory	25/9
Maximum dose of repeat GKRS	
60-70 Gy	13
70-75 Gy	21

GKRS - Gamma knife radiosurgery

68 years (range, 42-87 years). The median age of the initial symptom onset was 55 years (range, 36-71 years). The median pain duration prior to initial GKRS was 63 months (range, 5-169 months).

Radiosurgical techniques

All patients were treated with a ^{60}Co gamma unit by a team consisting of a radiation neurosurgeon and a medical engineer. Under local anesthesia, a stereotactic coordinate frame was attached to each patient's head. Then, MRI (Philip 1.5-tesla magnetic resonance scanner) scans were acquired by use of axial T1-weighted sequence and 0.8-mm slice thickness within the frame to identify the TN root entry zone. The MRI data were entered into the treatment planning computer, through which the conformal radiation plan was produced.

Using a 4-mm collimator, a single isocenter or two isocenters were positioned 3-4 mm anterior to the region where the sensory root of the TN exits the pons. The number of isocenters selected was related to the length of the TN root entry zone for reducing the influencing region. Five patients were treated with two isocenters. The isocenter was placed so that the 60% isodose line covered the entire target segment and there was no greater than 20 Gy radiations at the brainstem. At the first radiosurgical procedure, the mean dose was 73.4 Gy (range, 60-80 Gy) to the cisternal TN. At the second radiosurgical procedure, the patients were divided into two groups. In the first group of 13 patients, we selected a mean dose of 66.2 Gy (range, 60-70 Gy) to decrease the complications of the operation and the isocenter was the same as in the first procedure [Figure 1-left]. Later, we placed the isocenter 1-2 mm anterior to the first isocenter as Hasegawa *et al*.[12] reported [Figure 1-right]. In this way, the first target and the additional length of the nerve received adequate additional irradiation, while the brainstem received less irradiation. In the second group, the mean dose was 73.1 Gy (range, 70-75 Gy).

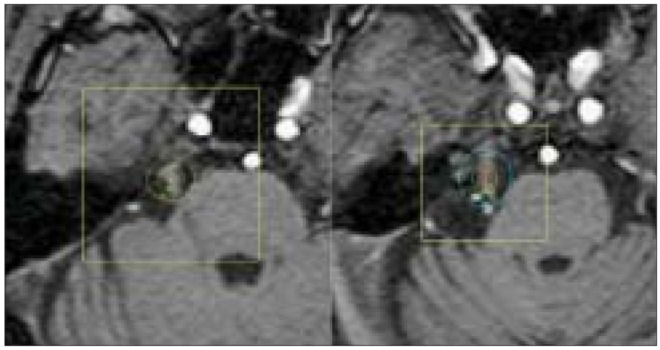

Figure 1: Axial T1-weighted MRI scan demonstrated the designated target of the second group (right, two isocenters, dose 70-75 Gy) was anterior to the first group (left, one isocenter, dose 60-70 Gy). The red ring represents the designing target. The yellow cross represents the target isocenter. The margin dose on the surface of the pons was less than 20 Gy

Follow-up and statistical analysis

Patients were discharged within 24 h after radiosurgery. All patients were subsequently evaluated by physicians who did not participate in the treatment via telephone or questionnaires six months after GKRS and then yearly. The mean interval of time between the initial and repeat GKRS was 17.4 months (range, 8-34 months) and the follow-up time was 21.6 months (range, 7-41 months) after the second radiosurgical procedure.

Patients were studied according to their degree of pain relief, use of medications and sensory disturbances, including corneal anesthesia and ocular complications. The Barrow Neurological Institute (BNI) scoring system was used to label the degree of pain relief as follows: Grade I, no pain and no medication required; Grade II, occasional pain and no medication required; Grade IIIa, no pain and continued use of medications required; Grade IIIb, some pain which was adequately controlled on medication; Grade IV, pain improved but not adequately controlled on medication; and Grade V, no pain relief whatsoever. If pain returned to the level of the poor category (i.e., BNI IV or V) after an initial significant improvement, we considered it to be recurrent pain. And if pain keeps at the level of the poor category (BNI IV or V) after surgical improvement, we considered it as refractory TN. Patients who achieved complete or partial pain relief, but continued to take some medications for fear of recurrent pain or achieved mild pain control (i.e., better than BNI IIIb) after radiosurgery were categorized as having a successful operation and the patients who obtained the best pain relief (i.e., BNI I) were categorized as having an excellent outcome.

The toxicity grade was rated on a four-point scale: Grade I, no facial numbness and no related neurological symptoms (including headache, vertigo, vomiting and other cranial nerve deficits) and symptomatic radiological changes; Grade II, mild facial numbness but not bothersome and/or mild neurological symptoms (including headache, vertigo, vomiting and other cranial nerve deficits) and symptomatic radiological changes which could be controlled by some outpatient medications; Grade III, facial numbness that was somewhat bothersome and/or moderate neurological symptoms (including headache, vertigo, vomiting and other cranial nerve deficits) and symptomatic radiological changes which could be alleviated by some outpatient medications; and Grade IV, facial numbness that was very bothersome and/or severe neurological symptoms and symptomatic radiological changes which required surgical intervention. The medications used or the surgical procedures after repeat GKRS for each patient were recorded in the computer for analysis.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), Version 11.5. Fisher's exact test, the log-rank test and the χ^2-test were used to analyze the data. All tests were two-tailed and a probability value <0.05 was considered significant.

Results

The outcome of patients with TN undergoing repeat GKRS is summarized in Table 2. Pain relief occurred in nearly all 34 patients after repeat GKRS. The median time of pain relief was eight weeks (range, 1-17 weeks). Fourteen patients (41.2%) were completely pain-free (BNI Grade I), four patients (11.8%) stopped all medications, but occasionally experienced slight pain (BNI Grade II), nine patients (26.5%) were pain-free, but still used medication for fear of pain recurrence (BNI Grade IIIa) and two patients (5.9%) continued to rely on medications to control the syndrome adequately (BNI Grade IIIb), yet the dose of medicine was less than before. A successful operation occurred in 29 of the 34 patients (85.3%) after repeat GKRS; the remaining four patients (11.8%), including two patients with recurrent symptoms three and seven months after the repeat procedure, experienced some symptomatic improvement, but still needed additional treatment (BNI Grade IV). One patient (2.9%) had no pain relief and had the same symptoms as before radiosurgery (BNI Grade V). Three of those patients who achieved poor results underwent MVD and partial rhizotomy after the repeat procedure. One patient had good pain relief (BNI Grade II) and the other two had a fair response, but needed some medications (BNI Grade IIIb). One patient who underwent repeat MVD, two separate glycerol rhizotomies and one radiofrequency rhizotomy after the repeat GKRS, achieved a little pain relief, but not completely after these procedures and endured permanent facial numbness (Grade III). One patient, who had no pain relief after the repeat procedure, refused any additional treatments and was lost to follow-up after 10 months. Two MS-TN patients had pain relief after repeat GKRS (BNI Grade IIIb) and required decreased doses of medication for pain control.

Table 2: The outcome of patients with trigeminal neuralgia who underwent repeat gamma knife radiosurgery

Outcome after repeat GKRS	Recurrent/ refractory		No. of procedure		
	Recurrent	Refractory	0	1-2	>3
Grade I	13	1	7	4	3
Grade II	4	0	1	2	1
Grade IIIa	4	3	4	1	2
Grade IIIb	3	1	0	3	1
Grade IV	1	3	1	0	3
Grade V	0	1	0	0	1
Excellent	13	1	7	4	3
Success	24	5	12	10	7
Poor	1	4	1	0	4
Total	25	9	13	10	11

The outcome of the operation was evaluated by BNI scoring system. Pain returning to the poor level (BNI IV or V) was considered as recurrent pain. And if pain keeps at the level of the poor category (BNI IV or V) after surgical improvement, we considered it as refractory TN. Patients who achieved outcome better than BNI IIIb were categorized as success

Among the 13 patients with no previous procedures before the initial GKRS, 12 patients (92.3%) achieved successful outcomes, including seven patients (53.9%) with excellent pain relief after repeat radiosurgery. By way of comparison, of the 21 patients with one or more prior surgical procedures before the repeat GKRS, 17 patients (81.0%) achieved successful outcomes, including seven patients (33.3%) with excellent pain relief. However, the difference between the two groups was not statistically significant (P = 0.377, log-rank test, $\upsilon = 1$). Compared with the 11 patients with more than three prior surgical procedures before the repeat GKRS, of which seven patients achieved successful outcomes, the difference was statistically significant (P = 0.042, log-rank test, $\upsilon = 2$).

Twenty-four of 25 patients (96.0%) who had recurrent pain after the first procedure achieved a successful operation and five of the nine patients (55.6%) who had no significant relief after the first procedure achieved a successful operation. The difference was statistically significant (P = 0.006, Fisher's exact test; P = 0.003, log-rank test, $\upsilon = 1$). Two patients with no pain relief after the initial GKRS reported unsuccessful outcomes after repeat GKRS as well. The outcome of patients who had 60-70 Gy radiation in the second treatment had no difference in outcome from those who had 70-75 Gy radiation (P = 0.17, $\upsilon = 1$).

Only four patients (11.8%) developed facial numbness after a repeat procedure. No other neurological symptoms and symptomatic radiological changes appeared. One patient reported continued trigeminal numbness after the initial GKRS, which did not worsen after the repeat procedure and was described as somewhat bothersome (Grade III). The remaining three patients with new facial numbness were described as mild, but not bothersome (Grade II) and the symptoms gradually resolved spontaneously in one to six months. Moreover, one of the patients with mild facial numbness had experienced similar symptoms after the first GKRS, but it was not bothersome and gradually resolved spontaneously in three months. No severe complications (i.e. more severe than Grade III) were reported.

Discussion

In this paper, we describe a retrospective analysis of clinical data from 34 patients who had refractory or recurrent TN and underwent repeat GKRS. The results indicated that the more surgical procedures the patients underwent prior to repeat GKRS, the worse the clinical outcome. The patients who had a good response following initial GKRS may therefore achieve a better result after a repeat procedure.

Being a newer treatment alternative since Leksell's[1] report, GKRS has more than an 80% probability of significant pain relief with a 10% or less risk of subsequent mild facial numbness or dysesthesia.[2,5,10,14-25] Thus, radiosurgery has gradually been regarded as a more efficacious procedure than MVD, radiofrequency rhizotomy, glycerol rhizotomy, balloon compression or radiofrequency ablation as an initial treatment for idiopathic trigeminal neuralgia.[14,26-34] Nevertheless, recurrent or refractory pain inevitably occurs. Thus, choosing the optimal modality after treatment failure continues to pose a dilemma for patients and physicians.

Hasegawa *et al*.[12] described 23 of 27 patients who achieved a successful outcome after repeat GKRS. Two of four patients who had recurrent pain obtained relief following additional procedures. The results were similar to the results of Pollock *et al*.[35-36] in which 14 of 19 patients with persistent TN continued to have an excellent outcome after repeat GKRS. Two patients had recurrent pain seven and 22 months after a repeat procedure. Both the patients had undergone more than five procedures, including GKRS, before or after repeat GKRS. Moreover, the results reported by the other authors are remarkably similar, as summarized in Table 3. These results demonstrated that repeat GKRS may be useful for some patients who have recurrent or refractory pain.[12,35-39]

According to the previous study, there may be some relationship between the outcome of repeat radiosurgery and the number of times the procedure was performed. In this study, we used 60-75 Gy for repeat GKRS. The difference between the successful patients (92.3%) who had no prior procedures before the initial GKRS and the successful patients (80.1%) who underwent more than one procedure before the initial GKRS was not significant. However, when compared with the successful patients (63.6%) who underwent more than three procedures before repeat GKRS, the difference was statistically significant ($P = 0.042$). Because the initial GKRS could be considered as a prior procedure to the repeat procedure, the latter result carries more weight. These patients were similar to Pollock *et al*.'s cohort;[40] excellent outcomes were achieved after radiosurgery in 67% of the patients who did not undergo previous surgery, compared with 51% of patients who underwent prior surgery. It was demonstrated that patients who had not undergone surgery previously had a significantly better outcome than patients who had undergone prioroperations before the repeat GKRS for idiopathic trigeminal neuralgia.

In the present study, success occurred in 24 of 25 patients (96%) who had recurrence after the first GKRS, compared with five of nine patients (55.6%) who were refractory after the initial treatment. Both the Fisher exact and log-rank tests were statistically significant ($P < 0.01$), suggesting that the patients who achieved good responses following the first procedure received a better result than those who were refractory for the first procedure after repeat treatment, but some controversy persists. Herman *et al*.[38] reported that among the 15 patients (83%) with recurrent pain after initially successful GKRS, 14 patients (93%) achieved excellent or good outcomes after repeat radiosurgery; all three patients with poor responses after initial GKRS reported poor outcomes after repeat GKRS. However, Brisman[37] reported that the difference was not statistically significant. In his cohort, a successful second GKRS occurred in 21 of 29 patients who had excellent or fair pain relief following the first GKRS and in seven of 15 patients who had a poor result following the first GKRS. He suggested the result may indicate that patients who have better pain relief initially after the first procedure have no or fewer prior procedures before radiosurgery. In addition, Pollock *et al*.[36] found that there is no relationship between excellent outcomes

Table 3: Series reports of repeat gamma knife radiosurgery for trigeminal neuralgia

Series	No.	Repeat dose (Gy)	Follow-up (mon)	Excellent (%)	Success (%)	Toxicity (%)	Prior surgery (%)
Hasegawa[12]	27	64.4	20.4	19	85	11	82
Pollock[36]	19	76	24	74	95	58	/
Brisman[37]	44	40	15	22	62	13	52
Herman[38]	18	70	24.5	45	78	11	28
Shetter[39]	19	46.6	13.5	53	85	42	/
Present	34	70	21.6	41	85	15	62

No. - Number. Patients who achieved outcome better than BNI IIIb after radiosurgery were categorized as having a successful operation and the patients who obtained the best pain relief (BNI I) were categorized as having excellent outcome after repeat radiosurgery and excellent outcomes after the initial procedure; however, in their data, there were only two patients who had persistent facial pain after the first procedure and the different conclusion from Brisman's report[37] may result from the different radiation dose (40 Gy vs. 60-75 Gy in the current report) delivered to the patients for repeat GKRS.

The radiation dose of the repeat GKRS treatment in the available clinic reports varies from 35 to 90 Gy.[1,5,12,13,35-39] According to the previous studies, pain relief and the incidence of facial numbness after GKRS correlate with the dose of treatment. The higher the treatment dose delivered, the better the pain relief achieved and unfortunately the higher the associated toxicity. Pollock *et al*.[35] indicated that patients treated with 70 Gy required additional surgery (37%), which is more often than patients treated with >70 Gy (13%); however, the incidence of new facial numbness or paresthesias was 8% compared with 32%. The result was similar to the other reports.[23,36,37] On the other hand, the patients who underwent multiple surgical prior procedures would have obtained a worse pain outcome and enhanced the difficulty of treatment. These might not be all related to the dose of the radiation of the first and repeat GKRS procedures.

Finally, it is worth pointing out that although similar reliable statistical conclusions have been achieved in the present study and in other previous reported results, the investigation on the GKRS treatment for refractory and recurrent TN is not over, especially considering that the numbers of the cohorts reported so far are not big enough. Extended research with large sample size is necessary to further clarify the key factors affecting the outcomes of repeated GKRS and optimize the treatment procedure.

Conclusion

Repeat GKRS for TN has been shown to be an efficient noninvasive surgical procedure with a low complication rate and is more likely to relieve pain in those who did not have a prior procedure or who had fewer than three procedures prior to their first GKRS. The dose selection is important such that the higher the dose used in treatment, the better the result can be achieved and the higher the incidence of facial numbness one may endure. Moreover, it seems that patients who had a good response following initial GKRS would achieve better results after a repeat procedure.

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