Gamma knife surgery for trigeminal neuralgia: improved initial response with two isocenters and increasing dose

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Object. The authors sought to evaluate the initial response of trigeminal neuralgia (TN) to gamma knife surgery (GKS) based on the number of shots delivered and radiation dose.

Methods. Between September 1998 and September 2003, some 63 patients with TN refractory to medical or surgical management underwent GKS at Upstate Medical University. Ten patients had multiple sclerosis and 25 patients had undergone prior invasive treatment. Gamma knife surgery was delivered to the trigeminal nerve root entry zone in one shot in 27 patients or two shots in 36 patients. The radiation dose was escalated to less than or equal to 80 Gy in 20 patients, 85 Gy in 21 patients, and greater than or equal to 90 Gy in 22 patients. Pain before and after GKS was assessed using the Barrow Neurological Institute Pain Scale and the improvement score was analyzed as a function of dose grouping and number of shots.

Sixty patients were available for evaluation, with an initial overall and complete response rate of 90% and 27%, respectively. There was a greater improvement score for patients who were treated with two shots compared with one shot, mean 2.83 compared with 1.72 (p < 0.001). There was an increased improvement in score at each dose escalation level: less than or equal to 80 Gy (p = 0.017), 85 Gy (p < 0.001), and greater than or equal to 90 Gy (p < 0.001). Linear regression analysis also indicated that there was a greater response with an increased dose (p = 0.021). Patients treated with two shots were more likely to receive a higher dose (p < 0.001). There were no severe complications. Five patients developed mild facial numbness.

Conclusions. Gamma knife surgery is an effective therapy for TN. Initial response rates appear to correlate with the number of shots and dose.

Key Words • gamma knife surgery • trigeminal neuralgia • dose escalation • radiosurgery

TRIGEMINAL neuralgia can be debilitating. Most patients receive medical therapy as the first-line management. If medical therapy is unsatisfactory additional interventional treatment modalities may be necessary. These include percutaneous rhizotomy, balloon compression, and craniectomy with microvascular decompression of the trigeminal nerve. These procedures are quite effective but are associated with significant risks and potential long-term complications. These potential risks, particularly in elderly patients, make less invasive techniques such as stereotactic radiosurgery particularly attractive.

Radiosurgery was first used by Leksell more than 50 years ago to treat TN but was not reported on until 1971. More recently authors of publications about GKS, when using a maximum dose of 70 to 80 Gy with 4-mm collimators, have reported initial response rates of 75 to 90% and complete pain relief in 58 to 70% of patients. Associated side effects were few and minor, with facial numbness being the most common. Response rates have been reported to last as long as 5 years in approximately 55% of patients. Trigeminal neuralgia is one of the most rapidly evolving indications for stereotactic radiosurgery. In an attempt to further improve pain relief, there has been a tendency to increase the maximum dose delivered. A dose of 90 Gy has been reported to be safe and effective. Response rates are improved with doses greater than 70 Gy, although dose–response comparisons at higher levels are limited. The volume of the trigeminal nerve included in the treatment volume was also studied in an attempt to improve pain relief further. The results of a single prospective randomized trial failed to reveal a benefit for two- compared with one-isocenter radiosurgery and the authors found a nonsignificant increase in complications.

During the past 5 years, we have gradually increased the GKS dose to greater than 90 Gy. In addition, a greater volume of the trigeminal nerve has been irradiated with two-isocenter dose plans in more recent patients. The purpose of
this study is to review our initial experience with GKS for TN and to analyze the results based on the radiation dose and the number of shots delivered.

Clinical Material and Methods

Patient Characteristics
Between September 1998 and September 2003, some 63 patients with TN refractory to medical, and in many cases, surgical therapy underwent GKS. No patient had undergone previous stereotactic radiosurgery. Patients had typical symptoms of TN, and 13 patients (21%) also reported atypical pain. The median age of the patients was 56 years (range 19–84 years) and 45 patients (71%) were women. Ten patients had a history of multiple sclerosis. The most common distribution of pain was in the second division of the trigeminal nerve, or in the second and third divisions together. The pain was on the right side in 34 patients, on the left in 28, and on both sides in one. Twenty-five patients (40%) had undergone prior invasive procedures, and 15 of these patients had undergone two or more previous surgical procedures. Of the patients who had undergone previous surgery, 72% had a sensory disturbance prior to GKS. All patients were initially assessed with a neurological examination and MR imaging. Clinical and imaging records were obtained from medical records, referring physicians, radiological studies, and the Gamma Knife Center database. All patients were assessed to have either idiopathic TN or neuralgia associated with multiple sclerosis.

Radiosurgery Technique
All patients were treated with the Gamma Knife model B unit (Elekta Instrument AB, Stockholm, Sweden) by a team consisting of a neurosurgeon, radiation oncologist, and medical physicist. After application of a local anesthetic a Leksell stereotactic coordinate frame was affixed to the patient’s head, and contrast-enhanced MR imaging was performed to display the region to receive the GKS treatment. Treatment planning was performed using Leksell GammaPlan (Elekta Instrument AB).

During the 5-year study period the maximum dose was increased over a range between 70 Gy and 95 Gy. The distribution of maximum dose is shown in Fig. 1. The dose plan consisted of distributing the radiation dose within the trigeminal nerve and ensuring that the 50% isodose line lay outside the brainstem. In 27 patients this was done through a single isocenter placed adjacent to the trigeminal nerve exit from the pons. This isocenter was adjusted to ensure the 50% isodose line was correctly placed. In 35 patients two isocenters were used. In these cases the second isocenter was placed 3 to 4 mm more distally along the trigeminal nerve and away from the brainstem and from the first isocenter. This arrangement yielded a more oval dose distribution and included a greater volume of trigeminal nerve within the high-dose area. Again, the dose plan was adjusted to ensure that the 50% isodose line lay outside the brainstem. The dose distributions for plans with one and two isocenters are depicted in Fig. 2.

Follow-Up Evaluation and Statistical Analysis
Patients underwent routine follow up performed by the Gamma Knife team, and pain, facial sensation, medication

![Fig. 1. Graph showing the distribution of GKS dose escalation from 70 to 95 Gy for the study population.](image1)

![Fig. 2. Gamma knife surgery plans for one-shot compared with two-shot treatment showing the 10-Gy (outer) and 50% isodose lines (inner) and dose–volume histograms of the pons.](image2)
usage, and neurological examinations were recorded. Pain was assessed using the BNI Pain Scale before and after GKS to determine the response to treatment (Table 1). The score (I–V) was converted to a linear scale and the improvement score was calculated as the difference between the pre- and post-GKS score. All patients were BNI Class IV or V prior to GKS. Sixty patients (95%) were available for evaluation; three patients were lost to follow up. The median follow up was 10 months (range 3–63 months). A response was defined as an improvement in the BNI score, and a complete response was defined as BNI Class I (pain free without medications). Responses were compared using paired t-tests of the pre- and posttreatment BNI score for each patient. The data were then analyzed as a function of radiation dose and the number of shots. The dose was grouped into three categories for the analysis of dose escalation: less than or equal to 80 Gy, 85 Gy, and greater than or equal to 90 Gy with 20 patients available for evaluation in each category. Dose was also studied without grouping by parametric analysis using linear regression.

Results

Fifty-four patients (90%) responded to GKS, with a median time to response of 1 month (range 1 day–3 months). Sixteen patients (27%) had a complete response to treatment (BNI Class I). One third of the patients were able to discontinue medications. Two of the 10 patients with multiple sclerosis had no response to GKS. The improvement score was greater for patients who were treated with two shots compared with one shot, mean 2.83 compared with 1.72 (p = 0.003). Patients who received a higher dose had a greater response to GKS (Fig. 3), and there was an increase in the improvement score at each dose escalation level: less than or equal to 80 Gy (p = 0.017), 85 Gy (p < 0.001), and greater than or equal to 90 Gy (p < 0.001). Linear regression analysis of dose compared with improvement score (Fig. 4), revealed a greater response with increased dose (p = 0.021). There was an interaction between dose and number of shots because patients treated with two shots were more likely to receive a higher dose (p < 0.001). Patients receiving one shot had a mean maximum dose of 79.1 Gy. Patients receiving two shots had a mean maximum dose of 88.3 Gy.

Ten patients developed a recurrence of their pretreatment TN pain during the follow-up period, with a median time to recurrence of 6 months. Eight of these patients were treated with repeated GKS. Of the patients with recurrent pretreatment pain after GKS, eight of 10 had prior invasive procedures for TN. Pain recurrence had no relationship to GKS dose. Patients with multiple sclerosis were not more likely to develop pain recurrence, although only 16% of the patients had multiple sclerosis in our study.
New onset trigeminal nerve dysfunction developed in five patients (8%), and all cases were described as mild and not bothersome. Only one of these five patients underwent two-shot GKS with a dose of more than or equal to 90 Gy. No patient developed facial dysesthesia or any other complication after GKS.

Discussion

Gamma knife surgery would seem to be an effective therapy for TN: the majority of patients experienced improvement in pain with low morbidity during the follow-up period. In this series, all except six of the patients available for evaluation responded to treatment, with an initial response rate of 90%. This result is comparable to those in other recent series, although the proportion of patients who achieved a complete response (27%) is somewhat less. We did include patients with multiple sclerosis, and these patients often have a lower response rate and have been excluded from some series. Prior invasive procedures can also affect the response to GKS, and over 40% of our patients had been refractory to surgical management.2

The maximum dose was gradually increased to an upper level of greater than or equal to 90 Gy. We found an incremental increase in response to GKS with dose escalation, both on linear regression analysis and on dose groupings of less than or equal to 80 Gy, 85 Gy, and greater than or equal to 90 Gy. Kondziolka, et al., found doses greater than or equal to 70 Gy to be more effective than doses less than 70 Gy but direct comparisons of GKS dose at the higher levels reported here have not previously been published. Two-isocenter dose plans were associated with a greater response to GKS in our series. The volume of the trigeminal nerve irradiated was previously addressed by Flickinger, et al., in a prospective randomized study. They did not detect a difference in pain relief with one shot compared with two shots, and there was no significant increase in treatment-related complications. Although their series is one of the few prospective reports on TN, patients received a modest maximum dose of 75 Gy. Because our study design introduced double-isocenter dose plans at a time when the dose was being increased, patients treated with two shots were more likely to receive a higher radiation dose, perhaps accounting for the difference in outcomes. We did not find more severe complications with the higher dose levels or two shots, although longer follow-up study is necessary. The recurrence of pain was also not related to the maximum dose delivered. The rate of new or increased numbness was similar to those found in other series, ranging from 8 to 16%.7,11,12

Conclusions

There is evidence for a relationship between dose and pain relief in the treatment of TN with GKS. Using two shots may also increase the response rate to this treatment.