CyberKnife radiosurgery for idiopathic trigeminal neuralgia

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Object. Gamma knife surgery is an accepted treatment option for trigeminal neuralgia (TN). The safety and efficacy of CyberKnife radiosurgery as a treatment option for TN, however, has not been established.

Methods. Forty-one patients were treated between May 2002 and September 2004 for idiopathic TN at Stanford University and the Rocky Mountain CyberKnife Center. Patients with atypical pain, multiple sclerosis, or previous radiosurgical treatment or a follow-up duration of less than 6 months were excluded. Patients were evaluated for the level of pain control, response rate, time to pain relief, occurrence of hypesthesia, and time to pain recurrence with respect to the length of the nerve treated and the maximum and the minimum dose to the nerve margin.

Thirty-eight patients (92.7%) experienced initial pain relief at a median of 7 days after treatment (range < 24 hours–4 months). Pain control was ranked as excellent in 36 patients (87.8%), moderate in two (4.9%), and three (7.3%) reported no change. Six (15.8%) of the 38 patients with initial relief experienced a recurrence of pain at a median of 6 months (range 2–8 months). Long-term response after a mean follow-up time of 11 months was found in 32 (78%) of 41. Twenty-one patients (51.2%) experienced numbness after treatment.

Conclusions. CyberKnife radiosurgery for TN has high rates of initial pain control and short latency to pain relief compared with those reported for other radiosurgery systems. The doses used for treatment were safe and effective. Higher prescribed doses were not associated with improvement in pain relief or recurrence rate. The hypesthesia rate was related to the length of the trigeminal nerve treated.

KEY WORDS • trigeminal neuralgia • CyberKnife • radiosurgical rhizotomy • stereotactic radiosurgery • trigeminal nerve

Frame-based radiosurgery has been established as an effective treatment modality for TN.[9,19,24,32] The development of CyberKnife radiosurgery (Accuray, Inc., Sunnyvale, CA) in 1994[1,5] added a promising new treatment option for this disease. Using noninvasive head immobilization and advanced image-guidance technology, the CyberKnife dynamically tracks skull position and orientation during treatment, thereby ensuring targeting accuracy throughout the entire procedure,[29] and patients are spared the discomfort of frame fixation onto their skulls. CyberKnife radiosurgery offers the ability to deliver nonisocentric, conformal and homogeneous radiation doses to nonspherical structures such as the trigeminal nerve. Romanelli, et al.,[29] have reported preliminary results for the treatment of 10 patients with TN. Focusing on the early response to treatment, they described a 70% short-term response rate. Nevertheless, the long-term safety and efficacy of this technique, along with the ideal portion and length of the nerve for radiosurgical targeting and the optimal dose for good pain relief with minimal side effects have yet to be reported.

The purpose of our study was to evaluate the safety, efficacy, and side effects of CyberKnife radiosurgery for treatment of TN, with special attention paid to the risk of facial numbness. We present combined data from Stanford University (Stanford, CA) and the Rocky Mountain CyberKnife Center (Boulder, CO).

CLINICAL MATERIAL AND METHODS

Patient Selection

Forty-one patients treated for idiopathic TN at the two centers between May 2002 and September 2004 were included in this study. The patients' characteristics and outcomes were retrieved from a prospectively maintained da-

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Abbreviations used in this paper: BNI = Barrow Neurological Institute; CT = computerized tomography; GKS = gamma knife surgery; MR = magnetic resonance; MVD = microvascular decompression; TN = trigeminal neuralgia.

tabase. All individuals underwent pretreatment evaluation for the cause of their pain; this included clinical assessment, neurological examination, and MR imaging. Patients with atypical pain, multiple sclerosis, or previous radiosurgical treatment or a follow-up duration of less than 6 months were excluded from this analysis.

The cohort included 23 women (56.1%) and 18 men (43.9%), whose mean age was 68 years (range 39–92 years). The mean duration of symptoms prior to Cyber-Knife rhizotomy was 9.5 years (range 0.4–45 years). The patients' demographic characteristics, distribution of TN by nerve division, and laterality of pain are presented in Table 1.

All patients suffered pain that was refractory to medication therapy. In 13 patients (31.7%) previous surgical procedures had failed. This group included two patients who had undergone glycerol injection; one who had received a glycerol injection and thermal rhizotomy; two who had undergone glycerol injections and an MVD; two who had undergone balloon compressions and radiofrequency rhizotomy; two who had received radiofrequency ablations; and four who had undergone MVD only. Nine patients (21.9%) had experienced numbness prior to treatment; all nine had undergone one or more prior surgical procedures. The mean follow-up time after CyberKnife rhizotomy was 11 months (range 6–22 months).

Dose Planning

All patients underwent iohexol-enhanced cisternography with CT scans obtained in 1.25-mm contiguous slices for visualization of the trigeminal nerve in the prepontine cisternal space prior to treatment. The amount of intrathecal contrast used was 10 to 12 ml. The trigeminal nerve was readily identified on the planning workstation and a 5- to 12-mm segment of the nerve was marked as the target volume. Care was taken to keep the target volume 2 to 3 mm anterior to the brainstem root entry zone. The trigeminal ganglion was also given consideration as a critical structure to which the dose was minimized. A typical radiation plan produced using the Accuray Treatment Planning System is shown in Fig. 1.

TABLE 1

Demographic data in patients who underwent CyberKnife treatment for idiopathic TN*

Characteristic			Value (%)
no. of patients			41
female			23 (56.1)
male			18 (43.9)
mean age (yrs)			68
range			39–92
laterality:			
lt			17 (41.5)
rt			24 (58.5)
distribution:			
V1			1 (2.4)
V2			8 (19.5)
V3			10 (24.4)
V1	V2		4 (9.8)
V2	V3		16 (39.0)
V1	V2	V3	2 (4.9)

* V = fifth cranial nerve.

The radiation dose prescription was developed using an inverse planning algorithm in which both the minimum and maximum doses to the desired target were prescribed. The dose administered to the adjacent brainstem was minimized by keeping the 50% isodose line outside of the brainstem.

Treatment Protocol

Patients were placed supine on the treatment couch and immobilized using a previously constructed custom-made immobilization thermoplastic mask. During treatment, digitally reconstructed radiographs created from the CT dataset were compared to standard orthogonal skull x-ray films. This defined in three dimensions the spatial relationship of the radiosurgical target volume to the patient's actual position and orientation, and allowed for adjustments during therapy if the patient inadvertently moved. The ability of the CyberKnife to deliver precision therapy is illustrated in Fig. 2.

All patients were treated in a single session with a median maximum dose of 78 Gy (range 71.4–86.3 Gy), delivering a median marginal dose of 65.5 Gy (range 60–70 Gy). A 7.5-mm collimator was used for all treatments, but the shortening of the source-to-axis distance to 65 cm virtually reduces the collimator size to 6 mm.

Evaluation of Clinical Efficacy

Patients were evaluated for the level of pain control, response rate, time to pain relief, occurrence of hypesthesia,
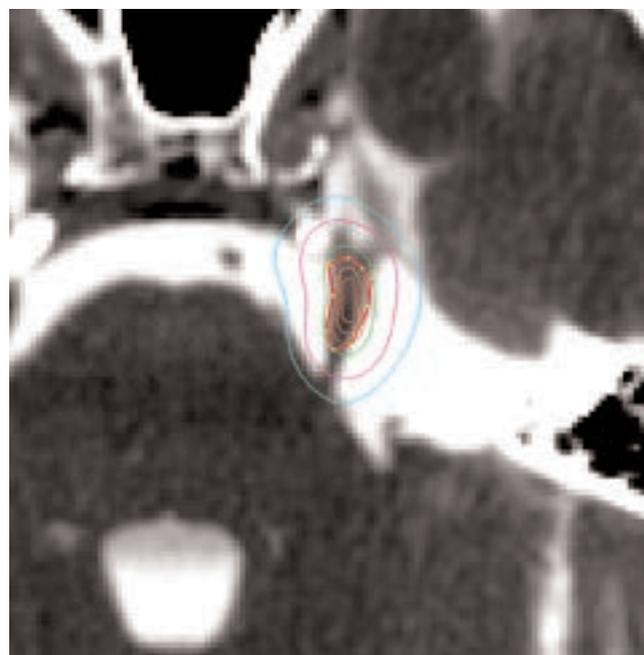

Fig. 1. A CT scan depicting a radiosurgery isodose distribution encompassing the anterior portion of the left trigeminal nerve in the prepontine cistern as revealed by iohexol cisternogram. The nerve segment contoured as target volume is shown by a *red line* connecting *yellow points.* A short segment of the nerve near the root entry zone is not included in the target volume. Surrounding isodose lines represent 25% *(light blue outermost line),* 50% *(magenta line),* 81% *(green line* at the nerve margin), 90% *(purple line),* 95% *(orange line),* and 98% *(red innermost line)* of the maximum nerve dose of 100%.
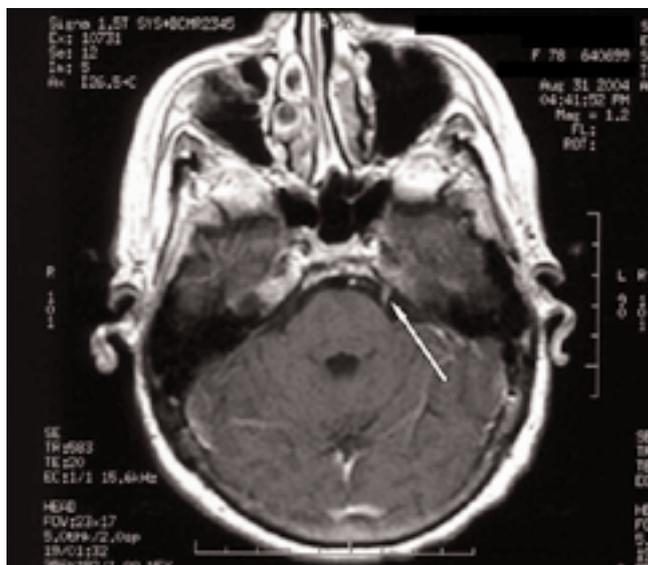
Fig. 2. Gadolinium-enhanced MR image demonstrating abnormal enhancement of the anterior portion of the nerve (arrow) and relative sparing near the dorsal root entry zone corresponding to the isodose distribution high-dose and lower-dose regions, respectively.

and time to pain recurrence with respect to the length of the nerve treated or the maximum and the minimum dose to the nerve margin used for the treatment.

The Boulder-Stanford Pain Scale was developed by two of the authors (M.L. and A.T.V.) according to the patient's self assessment level of pain and was reported as follows: I, excellent (90% pain relief, completely off pain medications); II, moderate (50% pain relief but < 90%, reduction in use of pain medications); III, mild (< 50% relief, no change in use of pain medications); or IV, no change in symptoms. More than 50% pain relief was considered a successful treatment.

Side effects such as sensory impairment (hypesthesia and anesthesia dolorosa) were evaluated while noting the time of occurrence, distribution in relation to the treated area, and severity. The BNI facial hypesthesia scale and scoring system[28] was used as follows: BNI Score I, no facial numbness; Score II, mild facial numbness, not bothersome; Score III, facial numbness, somewhat bothersome; and Score IV,

facial numbness, very bothersome. The mean score was calculated by assigning numerical values to the pain control levels or facial numbness levels.

Statistical Methods

Patients were grouped for statistical analysis according to the maximum administered dose, the minimum dose administered to the nerve margin, and the length of nerve treated. Patients were divided into two groups according to the maximum delivered dose; Group 1 received a maximum dose of 71.4 to 79.5 Gy (median 77.7 Gy) and Group 2 received a maximum dose of 80 to 86.3 Gy (median 81 Gy). Patients were also divided into two groups according to the minimum dose to the nerve margin used for the treatment; Group 1 received a minimum dose of 60 to 65.5 Gy (median 63 Gy) and Group 2 received a minimum dose of 66 to 70 Gy (median 67.5 Gy). A third category was created to evaluate the effect of length of the trigeminal nerve that was treated. Group 1 included patients with a treated nerve length of 5 to 6.5 mm (median 6 mm) and Group 2 were those with a treated nerve length of 7 to 12 mm (median 8 mm). Comparisons between the groups were made based on patient sex, age, duration of follow up, and the presence of preexisting numbness. Chi-square analysis was used to evaluate the distribution. T-tests were performed for statistical analysis and a probability value of less than 0.05 was considered significant.

RESULTS

Patient Characteristics and Treatment Parameters

The distribution of various factors among the groups of patients is presented in Table 2. Demographic values were similar in all patient groups with respect to sex, age, duration of follow up, and preexisting numbness. Only the number of patients in the maximum dose Group 1 was notably higher (p 0.025).

The median target volume measured 0.085 cm^3 (range 0.04–0.8 cm^3). The segment of the nerve encompassed by the 79% isodose line calculated by nonisocentric beam geometry averaged 7.2 mm in length (range 5–12 mm).

Pain Relief

Thirty-eight patients (92.7%) reported initially successful

TABLE 2
Demographic data and other factors with respect to
radiation dose and length of ner ve treated in patients with idiopathic TN*

Factor	Dmax (Gy)		Dmarg (Gy)		NL (mm)	
	Group 1 (71.4–79.5)	Group 2 (80.0–86.3)	Group 1 (60.0–65.5)	Group 2 (66.0–70.0)	5.0–6.5	7.0–12.0
no. of patients	29	12	23	18	15	26
age (yrs)	65.5	74.1	67.7	68.4	63.3	70.8
female	18	5	15	8	8	15
male	11	7	8	10	7	11
FU (mos)	10.7	12.1	11.6	10.4	9.1	12.2
preexisting numbness (%)	20.7	25.0	21.8	22.2	26.7	27.8

* Dmax = maximal dose; Dmarg = minimum marginal dose; FU = follow up; NL = length of nerve treated.

pain relief at a median time of 7 days (range < 24 hours–4 months) after CyberKnife treatment. Pain control was ranked as excellent in 36 patients (87.8%), moderate in two (4.9%), and three patients (7.3%) had no change in their symptoms at the follow-up visit, which ranged from 6 to 15 months posttreatment. For the three nonresponders, the length of trigeminal nerve targeted ranged from 5 to 7 mm and was treated to 73.2-, 77.3-, and 80.5-Gy maximum doses, respectively. Two of these patients had received no previous treatment and one had undergone an MVD and a glycerol injection. One patient had mild new numbness after the CyberKnife treatment and another had preexisting numbness after the MVD that remained unchanged after undergoing CyberKnife treatment.

The long-term response rate after a mean follow-up duration of 11 months was only 78% (32 of 41) compared with 92.7% initially. Six (15.8%) of the 38 patients with initially successful pain relief experienced a recurrence of pain at a median of 6 months (range 2–8 months) after treatment. All six had reported excellent pain relief initially. In addition to relapse of pain, two patients in this group had new hypesthesia, whereas four had unchanged preexisting numbness.

There was no statistically significant difference in pain response between the two groups of patients with respect to maximum dose (p = 0.9), minimum dose to the nerve margin (p = 0.8), or length of the nerve treated (p = 0.9). There was no statistically significant difference in the pain recurrence rate (p = 0.2, p = 0.8, and p = 0.3) with respect to the same variables.

Side Effects

A total of 30 patients (73.2%) had numbness at the follow-up time of 11 months; 21 (51.2%) reported new onset of symptoms after CyberKnife treatment. In nine of the 21 patients, their hypesthesia developed in the distribution of their original pain. In nine patients (21.9%), their numbness was preexisting but did not worsen after treatment.

The majority of patients rated their numbness as minor. Fifteen (71.4%) of the 21 patients with hypesthesia report-ed mild, not bothersome numbness, three (14.3%) reported moderate facial numbness, and three (14.3%) reported severe facial numbness. It is interesting to note that all but one of the 21 patients experienced excellent pain control, whereas the remaining patient reported no change in the pain. One patient with mild, not bothersome facial numbness and one with very bothersome numbness also had anesthesia dolorosa.

No statistically significant differences were observed in the degree of numbness between the two groups of patients with respect to the maximum dose (p = 0.2) or minimum dose to the nerve margin (p = 0.3). Nevertheless, the mean numbness score (1.3 compared with 2.0) was significantly less (p = 0.028) in the cohort in which the shorter nerve length of 5 to 6.5 mm (median 6 mm) was treated, compared with the 7 to 12 mm (median 8 mm) cohort (Fig. 3). Other complications included decreased corneal reflex in three patients, ipsilateral masticator weakness in one, and trismus in one.

DISCUSSION

Pain Relief

Various techniques are used in radiosurgery to achieve maximal pain relief and minimal complications. To date there has been only one publication with preliminary data on the treatment of TN with the CyberKnife.[29] In this study of 10 patients, Romanelli,, et al., reported an overall 70% response rate. Their first five patients were treated with a mean dose of 64.3 Gy delivered at the 80% isodose line. All five reported excellent initial pain relief, with a median latency to pain relief of only 24 hours (range 24–78 hours). In one patient, however, severe dysesthesias developed, and the dose was then decreased to 60 to 64 Gy delivered at the 80% isodose line in the remaining five patients. After the dose was lowered, only two of these five patients responded to treatment, with latency to pain relief taking as much as 2 months. From their results we infer that the CyberKnife could be an effective mode of therapy for treating
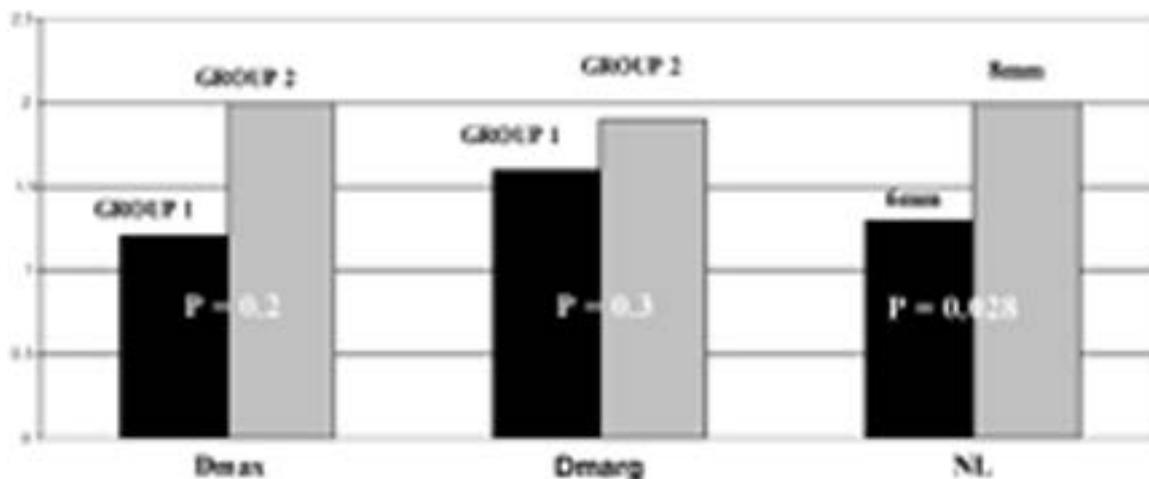

Fig. 3. Bar graph showing the posttreatment hypesthesia score assessment. Values on the y axis represent the mean facial numbness score (BNI scores were converted to Arabic numbers to permit averaging). Dmarg = minimum marginal doses; Dmax = maximum doses; NL = length of the nerve treated.

TN, and that a larger study would be required to identify optimal treatment doses.

In our series of 41 patients, we observed initially successful pain relief in 92.7% of cases, which is comparable to other modes of radiosurgery (50–96%).[12,13,17,32,36] It is interesting to note that the reported 96% response rates were observed in patients in whom radiosurgery was used as the initial therapy.[17]

In comparing the durability of our response to the other modalities, we too observed recurrences. In centers specializing in GKS it has been reported that only 45 to 55.8% of patients experienced sustained pain relief at 3 to 5 years posttreatment.[3,14,18,22,26,33] Even with other therapy modes, such as MVD, there exists a high rate of recurrence 5 to 10 years postintervention. In our study 78% of patients continued to report pain relief at a mean follow-up duration of 11 months, compared with the initial response rate of 92.7%. Whether we observe more relapses in our series will depend on the duration of follow up.

Optimal Dose

The optimal dose for treatment of TN is still undefined. Experimental studies in primate models have demonstrated focal axonal degeneration of the trigeminal nerve at a dose of 80 Gy and partial nerve necrosis at higher doses (100 Gy).[16] Some groups initially used doses closer to 90 or 100 Gy and reported an improved rate of pain relief[3,18,23,25,30] Using GKS, Pollock, et al.,[25] treated patients with a dose of 90 Gy, but found that the higher doses were associated with an increased rate of trigeminal nerve dysfunction. They reported a 54% rate of permanent trigeminal nerve dysfunction in patients treated with GKS at the maximum dose of 90 Gy, compared with previous reports of a 10% rate of trigeminal nerve dysfunction at doses closer to 80 Gy. Interestingly, these researchers' rate of new-onset numbness is comparable to that found in our study (51.2%). In examining our results, we found no association between numbness and different doses. In addition, we observed no correlation of efficacy with different doses. Nevertheless, we did observe a correlation of numbness to nerve length treated, which is discussed in more detail later.

Target Location

The optimal location for the radiosurgical treatment of TN is still controversial.[11,21,23,33] To address the burning component of the pain, even the centromedian nucleus of the thalamus has been used as a second radiosurgical target after treatment of the trigeminal nerve in cases of refractory postherpetic TN.[15] Kondziolka, et al.,[20] advocate keeping the target volume 2 to 3 mm anterior to the root entry zone to minimize exposure of the brainstem. Goss, et al.,[11] however, found a positive correlation between brainstem exposure to radiation and response rates. Because Kondziolka's group reported only 10% numbness, we opted to keep our target volume 2 to 3 mm anterior to the root entry zone. In addition, we used the previously described CT cisternography modality[29] for our treatment planning to obtain an accurate, distortion-free visualization of the trigeminal nerve. The drawback to the use of cisternography, however, is the inability to assess adjacent blood vessels compressing the nerve that might otherwise be identified with high-definition MR imaging.[4,7,35]

Side Effects and Complications

Hypesthesia is the most common complication reported after radiosurgery for TN.[26,27] As mentioned earlier, higher treatment doses have been linked to higher complication rates in the published literature.[11,25] Numbness or paresthesia has been reported to occur in 6 to 54% of patients[10,22,25,26,31,33,34] after treatment with frame-based radiosurgery. Bothersome dysesthesias were reported in 32% of cases, and 8% of patients with TN who were treated with a 90-Gy maximum dose experienced corneal numbness.[25] We have not found a statistically significant correlation between dose and numbness in our studies.

In addition, the onset to numbness is variable. Urgosik, et al.,[33] reported a 20% rate of numbness after initial therapy and 32% after repeated treatment at a median of 5 years of follow up, compared with only a 6% rate of numbness at a median of 19 months of follow up. Longer follow-up durations will be required to assess the numbness rate accurately in our study.

Flickinger, et al.,[10] also suggested that treatment of longer lengths of the trigeminal nerve is associated with more complications. Their study was a prospective randomized clinical trial in which patients with TN were divided into two treatment arms. Each group was treated with GKS; patients in one arm of the study were treated with one isocenter (mean nerve length 5.4 ± 0.4 mm) and in the second arm they were treated with two isocenters (mean nerve length 8.7 ± 1.1 mm). These authors found a higher complication rate (although it was not statistically significant) in the two-isocenter arm. The response rates between the two groups were not statistically different. The authors suggested that increasing treatment volumes did not improve pain relief, but did increase the rate of complications. Nevertheless, the issue of dose distribution homogeneity associated with the use of two partially overlapping isocenters and its possible relationship with increased complications was not addressed. In contrast, Alpert, et al.,[2] found the opposite results. They reported impressive improvement in pain reduction and a lower incidence of complications when they used two isocenters and a higher radiation dose. Their mean maximum dose was 88.3 Gy, and only 8% of their patients had mild hypesthesia at a median follow-up duration of 10 months.

The CyberKnife has the unique ability to deliver non-isocentric, homogeneous conformal irradiation to an extended length of trigeminal nerve. In addition, an important performance characteristic of the CyberKnife is the accuracy with which it can place the dose distribution. Application accuracy for the CyberKnife system is based on the accuracy of beam delivery, which combines the robot and the camera image tracking system with CT scans obtained for treatment planning. Overall, the clinical accuracy of CyberKnife treatments is 1.1 mm (standard deviation 0.31 mm) if a CT slice thickness of 1.25 mm is used for treatment planning.[6] We hoped to improve efficacy and latency to pain control by targeting a longer segment of the nerve, with the benefit of the improved accuracy and precision of the CyberKnife. Our results in terms of side effects were surprising; we found a statistically significant increase in the numbness score if the length of trigeminal nerve treated was increased to a median of 8 mm compared with 6 mm. This parallels findings reported by Flickinger, et al.[10]

Our results indicate that treating shorter portions of the trigeminal nerve will decrease the rate of numbness, and we have since modified our protocols to treat no more than a 6-mm length of the nerve.

Although based on a preliminary study and small sample size, the markedly brief latency to pain relief was striking.[29] The median time to pain relief reported after GKS varied from 3 weeks to 3 months,[18,19,22,24,33,34] or from 6 weeks to 2.7 months[8,11,32] after shaped-beam radiosurgery. We found a median latency to pain relief of only 7 days. A possible explanation for the short latency of response could be the non-isocentric technique used in treating the trigeminal nerve. Although no apparent association was seen between nerve length and latency, we did notice that lower doses were associated with longer latencies (this was not statistically significant).

CONCLUSIONS

Although studies conducted in a larger number of patients will be required to understand these associations better, CyberKnife radiosurgery might be a reasonable treatment option for patients with acute pain or for those who desire quick relief of their pain and who would otherwise undergo more invasive procedures. CyberKnife radiosurgery for TN treatment results in high rates of initial pain control and a short latency to pain relief. The doses used for treatment were safe and effective. Higher prescribed doses were not associated with better pain relief or a lower recurrence rate. The hypesthesia rate was related to the length of the trigeminal nerve treated.

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