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CYBERKNIFE RADIOSURGERY FOR TRIGEMINAL NEURALGIA TREATMENT: A PRELIMINARY MULTICENTER EXPERIENCE

OBJECTIVE: Radiosurgery has gained acceptance as a treatment option for trigeminal neuralgia. We report our preliminary multicenter experience treating trigeminal neuralgia with the CyberKnife (Accuray, Inc., Sunnyvale, CA).

METHODS: A total of 95 patients were treated for idiopathic trigeminal neuralgia between May 2002 and October 2005. Radiosurgical dose and volume parameters were retrospectively analyzed in relation to pain response, complications, and recurrence of symptoms. Optimal treatment parameters were identified for patients who had excellent and sustained pain relief with no complications, including severe or moderate hypesthesia.

RESULTS: Excellent pain relief was initially experienced by 64 out of 95 patients (67%). The median time to pain relief was 14 days (range, 0.3–180 d). Posttreatment numbness occurred in 45 (47%) of the patients treated. Using higher radiation doses and treating longer segments of the nerve led to both better pain relief and a higher incidence of hypesthesia. The presence of posttreatment numbness was predictive of better pain relief. The overall rate of complications was 18%. At the mean follow-up time of 2 years, 47 of the 95 patients (50%) had sustained pain relief, all of whom were completely off pain medications.

CONCLUSION: The results of this study suggest the following optimal radiosurgical treatment parameters for treatment of idiopathic trigeminal neuralgia: a median maximal dose of 78 Gy (range, 70–85.4 Gy) and a median length of the nerve treated of 6 mm (range, 5–12 mm).

KEY WORDS: CyberKnife, Radiosurgical rhizotomy, Stereotactic radiosurgery, Trigeminal nerve, Trigeminal neuralgia

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Trigeminal neuralgia (TN) is a common condition affecting approximately five out of 100,000 people who present with lancinating pain from one or more divisions of the trigeminal nerve. Compression of the trigeminal nerve at the root entry zone by a vascular structure such as the superior cerebellar artery is thought to be the most probable cause of demyelination and the subsequent pain. Anti-epileptic drugs are the first-line therapies. When medical therapies are exhausted, patients are left with a choice of surgical procedures. Although microvascular decompression (MVD) is considered the “gold standard” treatment for TN, it may not be suitable for elderly patients with high operative risks or those who are simply unwilling to

undergo surgery. Other invasive procedures such as glycerol or radiofrequency rhizotomy offer high rates of initial pain relief but are susceptible to high recurrence rates (6, 11, 35).

In the mid-1990s, several reports of the efficacy of frame-based radiosurgery for treating TN appeared (4, 15, 24, 34). The use of frameless radiosurgery for the treatment of TN was reported in 2003; these reports showed high rates of pain relief and short latencies to response (30, 31). However, this study contained only a small cohort of patients with limited follow-up. Long-term safety, efficacy, the ideal portion and length of the nerve to be radiosurgically lesioned, and the optimal dose for good pain relief with minimal side effects have yet to be established. We report our sub-

sequent, but still preliminary, multicenter experience using the CyberKnife (Accuray, Inc., Sunnyvale, CA) to treat TN. CyberKnife radiosurgery abrogates the need for a frame; intraoperative x-rays allow dynamic tracking of the target throughout the treatment to ensure targeting accuracy (3). Furthermore, nonisocentric treatment planning permits the delivery of a highly homogenous dose to nonspherical elongated structures such as the retrogasserian sensory root (5, 17).

The purpose of this study was to evaluate the safety and effectiveness of CyberKnife radiosurgery for TN treatment with special attention to the risk of facial numbness. The goal was to better define optimal dose and volume (length) parameters. Such factors were analyzed in relation to pain response, complications (except for mild hypesthesia), and recurrence of symptoms.

PATIENTS AND METHODS

Patient Selection

A total of 95 patients diagnosed with idiopathic TN and treated between May 2002 and October 2005 for TN pain at the Department of Neurosurgery at Stanford University School of Medicine (55 patients), the Rocky Mountain CyberKnife Center (10 patients), and the Department of Neurosurgery at Besta Neurological Institute (30 patients) with at least 12 months of follow-up were analyzed. The case characteristics for this retrospective study were retrieved from the patient charts, and clinical outcomes were assessed at a mean follow-up period of 23.5 months (median, 22.0 mo; range, 12–46 mo). Follow-up assessments were performed at outpatient visits or as phone interviews by clinical staff (MM, RB). Patients who had undergone previous stereotactic radiosurgery were not included in this analysis.

All patients underwent pretreatment evaluation for the cause of their pain, which consisted of clinical assessment, neurological examination, and imaging studies. Magnetic resonance imaging (MRI) and computed tomographic (CT) studies were performed to detect neurovascular compression, demyelinating disease, or cerebellopontine angle lesions. Only patients who became intolerant or refractory to medication therapy, had contraindications to surgery, or were unwilling to undergo anesthesia and surgery were offered this treatment.

Demographics

Ninety-five patients, including 55 women (58%) and 40 men (42%), were diagnosed with stabbing, paroxysmal pain typical of idiopathic TN. The average age of the patients was 69.8 years (range, 40–92 yr). The mean duration of symptoms before CyberKnife treatment was 8.4 years (range, 0.3–30 yr). Pain distribution and selected patient demographic characteristics are presented in *Table 1*. Thirty-five (37%) patients had unsuccessful previous surgical procedures (in some cases two or three), including MVD, radiofrequency or retrogasserian glycerol rhizotomy. Twenty-one (22%) patients had preexisting numbness before the CyberKnife treatment.

Treatment Planning

Thirty-two (28%) patients treated at Besta Neurological Institute had MRI scans (fast imaging using steady-state acquisition sequence) and contrast-enhanced CT scans fused for treatment planning. Eighty-one (72%) patients treated before 2006 at the Department of Neurosurgery at Stanford University School of Medicine and the Rocky Mountain

TABLE 1. Patient demographic data^a

	Idiopathic TN
Total no. of patients	95
Women	55 (58%)
Men	40 (42%)
Age (yr)	69.8 (40–92)
Duration of pain (yr)	8.4 (0.3–30)
Laterality	
Left	39 (41%)
Right	56 (59%)
Distribution or division	
V1	3 (3%)
V2	21 (22%)
V3	21 (22%)
V1 + V2	13 (14%)
V2 + V3	29 (31%)
V1 + V2 + V3	8 (8%)
V3 + shoulder	—
Tongue	—
Preexisting numbness	21 (22%)
Previous surgical procedures	35 (37%)

^aTN, trigeminal neuralgia. Values are presented as mean values and percentages/range in parentheses.

CyberKnife Center underwent contrast-enhanced CT cisternography with 1.25-mm contiguous slices for visualization of the TN in the prepontine cisternal space before treatment. Since then, CT/MRI fusion has been validated and implemented as a standard procedure at these centers (*Fig. 1*). Lumbar puncture was performed to inject contrast (iohexol, iopamidol). The trigeminal nerve was readily identified on the planning workstation, and a segment of the nerve was marked as the target volume (*Fig. 2*). The median target volume identified was 0.04 cm³ (range, 0.02–0.8 cm³). Care was taken not to extend into the gasserian ganglion within Meckel's cave; for that reason, the target volume was kept 2 to 3 mm from the dorsal root entry zone. Nonisocentric treatment plans were used. The dose to the brainstem was constrained to 30 to 50% of the nerve maximal dose.

Treatment

Patients were placed supine on the treatment couch and immobilized using a previously constructed, custom-made thermoplastic mask. Patient setup and target tracking were accomplished by comparing digitally reconstructed x-rays created from



FIGURE 1. Contrast-enhanced computed tomographic cisternography (axial view) showing the trigeminal nerve (arrow).

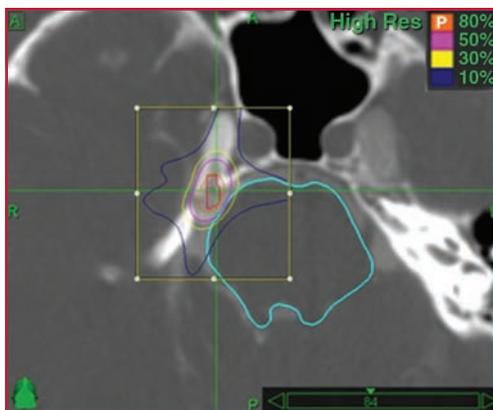


FIGURE 2. Typical treatment plan showing a red line demonstrating the nerve segment contoured as target volume with a short segment near the root entry zone excluded from the target volume. The brainstem, encircled with a light blue line, shows its relationship to the isodose curves. Surrounding isodose lines represent 10% (dark blue outermost line), 30% (yellow line), 50% (magenta line), and 80% (orange line at the nerve margin) of the maximum nerve dose of 100%.

the CT data set with standard orthogonal cranial x-rays taken after every three to five beams (typically every 30–180 s and up to 5 min) throughout the treatment. Up to 30 x-ray checks are performed during each radiosurgery. The dose from imaging is roughly equivalent to that of a diagnostic CT scan, resulting from the use of high-sensitivity digital imaging based on amorphous silicon detectors. The small patient (and target) movements were detected and new target coordinates sent to the robotic arm to adjust the aiming of the linear accelerator. Cranial position and orientation were reduced to less than 1 mm in the treatment space and less than one degree of rotation throughout the treatment delivery.

All patients were treated in a single session, which lasted from 60 to 90 minutes (the older G3 model was used for this group of patients). In an attempt to minimize hot spots and heterogeneity within the target, a nonisocentric beam treatment plan was used. This typically consisted of 50 to 70 focused beams delivered in segments, during which stereoscopic imaging to check the patient's position was performed every 30 seconds to 5 minutes. Collimators of either 5 or 7.5 mm diameter were used for this cohort of patients.

Treatment Parameters

The median target volume measured 0.04 cm^3 (range, 0.02–0.8 cm^3). The median treated segment of the trigeminal nerve was 6 mm in length (range, 3–12 mm).

Patients were treated with a median maximal dose (Dmax) of 75 Gy (range, 50–86.4 Gy) prescribed to a median 80% isodose line (range, 72–91%) and delivering a median marginal dose (Dmin) of 60 Gy (range, 40–70 Gy).

Clinical Outcome Evaluation

Response rates, pain control, latency to pain relief, recurrence, time to recurrence, and incidence of hypesthesia were collected and correlated with the length of the nerve treated, the Dmax, and the Dmin.

Pain control was assessed using the Boulder-Stanford pain relief scale (18), where 1 is excellent (>90% pain relief, completely off pain medications), 2 is moderate (>50% pain relief and <90% reduction in use of pain medications), 3 is mild (<50% relief, no change in use of pain medications), and 4 indicates no change in symptoms. Only excellent pain relief was considered a successful treatment, which indicated that patients were off any pain medications for TN. Recurrences were defined as return of pain to the previous level or to at least 3 on the Boulder-Stanford pain relief scale.

The Barrow Neurological Institute facial hypesthesia scale and scoring system (29) was used to assess numbness. According to this scale, I indicates no facial numbness, II indicates mild facial numbness that is not bothersome, III indicates somewhat bothersome facial numbness, and IV indicates very bothersome facial numbness. Other side effects, including paresthesia and dysesthesia, were evaluated along with their time of occurrence, distribution in relation to the treated area, and severity.

Statistical Methods

Logistic regression statistical analysis was performed to identify correlations among treatment parameters and clinical outcomes, durability of pain relief, and complications. The radiosurgical treatment parameters associated with optimal clinical results (excellent and durable pain control with minimal complications) were also identified. Cox regression analysis and *t* tests were used to accomplish this objective. An actuarial method (Kaplan-Meier statistical analysis) was also used to predict probability of sustained pain relief.

RESULTS

Pain Relief

Eighty-seven of the 95 (92%) patients reported some initial pain relief, but treatment was considered successful in only 64 (67%) patients. Seven (7%) patients had moderate pain relief, 16 (17%) patients had mild pain relief, and eight (8%) patients had none (Fig. 3). The median time to pain relief was 14 days (range, 0.3–180 d). Mild pain relief took significantly longer to

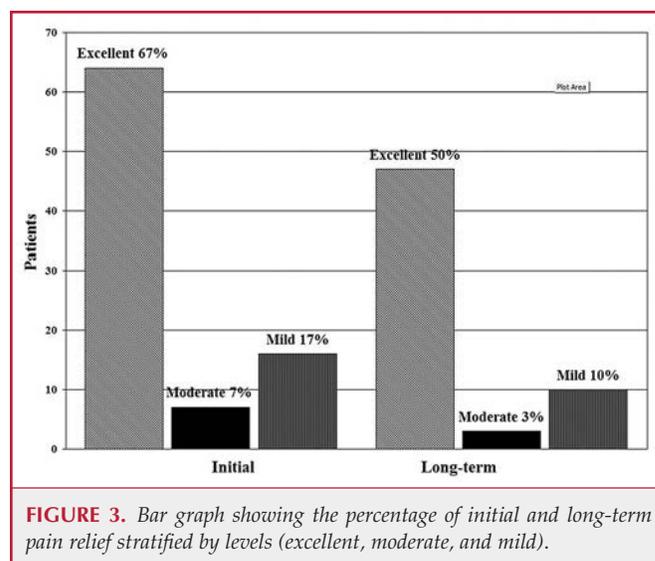


FIGURE 3. Bar graph showing the percentage of initial and long-term pain relief stratified by levels (excellent, moderate, and mild).

achieve than excellent or moderate relief, with the median time being 30 and 7 days, respectively (*t* test, *P* = 0.02).

Logistic regression analyses were performed to determine whether or not any of demographic factors or radiosurgical treatment parameters were predictive of better pain relief. No statistically significant correlations between pain relief and age, sex, laterality, duration of symptoms, or number of previous surgical treatments were obtained. Better pain relief was achieved when a longer segment of the trigeminal nerve was treated (*P* < 0.00001) and a higher Dmax (*P* = 0.02) or Dmin (*P* = 0.006) was used.

Side Effects

A total of 45 patients (47%) reported new posttreatment numbness on follow-up examination. Nineteen (20%) patients had mild, 15 (16%) had moderate, and 11 (12%) had severe numbness, as defined by the Barrow Neurological Institute facial hypesthesia scale. Two patients had symptoms of dysesthesia in addition to the symptoms of moderate facial numbness. The median time to develop numbness was 6 months (range, 1–14 mo).

Correlations between posttreatment numbness and demographic factors or radiosurgical treatment parameters were analyzed using logistic regression analyses. Age, sex, trigeminal pain distribution, and duration of symptoms were not predictive of numbness. Numbness increased with the number of previous surgical treatments (*P* = 0.003). There was also a higher occurrence of posttreatment numbness when a longer segment of the trigeminal nerve was treated along with higher Dmin and Dmax used (*P* < 0.00001).

Posttreatment numbness was predictive of better pain relief (*P* = 0.0003). Although none of the patients who had mild pain relief had any new numbness, there were two patients who had no pain relief and yet still had severe numbness; one of these patients also had diplopia. Two patients with moderate pain relief had mild numbness, and the rest of the new hypesthesia-related side effects occurred in patients with excellent pain relief.

The overall rate of complications was 18%. Side effects within the trigeminal nerve innervation area included decreased corneal reflexes (*n* = 4), anesthesia dolorosa (*n* = 2), trismus (*n* = 2), and masticator weakness (*n* = 2). Outside the trigeminal nerve innervation area diplopia (*n* = 1), decreased hearing (*n* = 2), dry eye syndrome (*n* = 2), and right foot paresis (*n* = 1) were observed. All of these complications occurred only in the early part of this series, and each of them is explained by an excessive dose, inclusion of the trigeminal ganglion in the target region, and poor planning. Treatment dose (approximately 20–30% of Dmax) inadvertently included an excessive portion of the brainstem in cases of decreased hearing and right foot paresis complications. There was no improvement of symptoms at the time of the last follow-up examination in these three patients. We have not had any complications related to the lack of headframe fixation or patient movement. There was one perioperative complication, a cerebrospinal fluid leak, associated with cisternography.

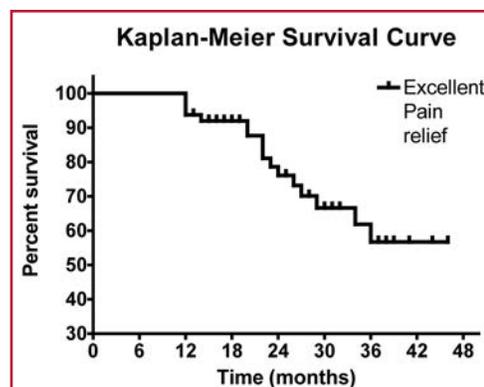


FIGURE 4. Kaplan-Meier curve showing the percentage of patients whose pain relief had not recurred as a function of time since treatment.

Long-term Results

Twenty-seven (31%) of the 87 patients who had any initial pain relief experienced a recurrence of their pain. The long-term response rate and successful treatment were achieved in 50% (47 out of 95 patients) after a mean follow-up time of approximately 2 years (Fig. 3). Therefore, treatment was considered successful for only 47 of the 64 patients who initially had excellent pain relief. Among the patients who had excellent long-term pain relief, eight also had severe and 15 had moderate numbness. Actuarial analysis (Kaplan-Meier statistical analysis) was used to demonstrate the durability of the results (Fig. 4). The 12-, 24-, and 36-month actuarial pain relief rates were 63, 55, and 50%, respectively.

Factors that may have influenced recurrence after initially successful treatment were analyzed using logistic regression analysis. Patients who experienced recurrence did not differ significantly from patients who did not with respect to demo-

TABLE 2. Comparison of selected demographic and radiosurgical treatment parameters for patients with recurrence and sustainable pain relief^a

Pain relief	Sustainable	Recurrence
Total no. of patients	50	27
Women	29	15
Men	21	12
Age (yr)	71.5 (42–92)	72.3 (40–86)
Duration of pain (yr)	8.6 (0.5–25)	7.8 (0.3–30)
Preexisting numbness	6 (12%)	9 (33.3%)
Previous surgical procedures	15 (30%)	12 (44.4%)
Median Dmax (range)	77.5 Gy (65–86.3)	65 Gy (50–86.4)
Median Dmin (range)	64 Gy (52–70)	52 Gy (40–70)
Median length of the nerve	6 mm (4–12)	4 mm (3–9)

^a Dmax, maximal dose; Dmin, marginal dose. Values are presented as mean values and percentages/range in parentheses.

TABLE 3. Comparison of selected demographic and radiosurgical treatment parameters^a

	Optimal	Other
Total no. of patients	22	73
Women	14	40
Men	8	33
Age (yr)	71.3 (42–88)	69.3 (40–92)
Duration of pain (yr)	8.5 (0.5–24)	8.4 (0.3–30)
Prior surgical procedures	9 (40.9%)	35 (35.6%)
Median Dmax (range)	78 Gy (70–85.4)	75 Gy (50–86.4)
Median Dmin (range)	62 Gy (56–70)	60 Gy (40–70)
Median length of the nerve	6 mm (5–12)	6 mm (3–12)

^a Dmax, maximal dose; Dmin, marginal dose. Values are presented as mean values and percentages/range in parentheses.

graphics, duration of symptoms, preexisting numbness, or number of previous surgical procedures (Table 2). Patients who had preexisting numbness were more likely to experience recurrence of their pain ($P = 0.012$). A longer treated segment of the nerve ($P = 0.0002$) and a higher Dmax and Dmin ($P < 0.00001$) were predictive of a lower recurrence rate. A higher recurrence rate was also correlated with lower posttreatment numbness ($P = 0.0001$).

Optimal Results

We reasoned that a comparison of the treatment of the patients who experienced optimal outcomes (excellent pain relief, no recurrences, no moderate or severe numbness, and no complications) with that of the patients whose outcomes were nonoptimal (i.e., patients who experienced less than excellent pain relief and/or greater than mild numbness or complications) would point to optimal treatment parameters (Table 3). Thirteen patients (59%) in the optimal outcome group noted mild and not bothersome hypesthesia. Logistic regression analysis was performed to reveal any significant correlations. None of the demographic factors were significantly different across the groups. Although the level of significance between the optimal outcome and nonoptimal outcome groups was generally smaller than in previous comparisons based on pain relief or complications alone, it was still true that a longer treated segment of the nerve ($P = 0.04$) and higher Dmax ($P = 0.01$) and Dmin ($P = 0.05$) were predictive of optimal clinical outcomes. Therefore, the following optimal radiosurgical treatment parameters were identified: the median Dmax was 78 Gy (range, 70–85.4 Gy) and the median length of the nerve was 6 mm (range, 5–12 mm) (Table 3).

DISCUSSION

Our initial results (18) with a smaller cohort of patients showed that posttreatment numbness correlated with length of the nerve treated but not the treatment dose. After treat-

ing more patients from additional centers and observing them for a longer duration of follow-up, we have a better understanding of the treatment parameters associated with outcomes and complications.

Pain Relief

We observed initial pain relief in 92% (87 out of 95) of the patients with idiopathic trigeminal pain. Sixty-seven percent (64 out of 95) of the patients reported excellent pain relief. Our results are consistent with the reported rates from studies of gamma knife (Elekta AB, Stockholm, Sweden) and linear accelerator (LINAC) radiosurgery, which have reported initial pain relief of 50 to 96% (9, 10, 13, 34, 39). These results are also consistent with our initial study of 41 patients in which we reported initial relief in 92.7% of the 41 patients (18). In contrast to our previous reports, the latency to pain relief in the current study was longer. Our previous series showed the median time to pain relief to be 7 days, whereas in our larger study, we observed a median time of 14 days for all responders. The increased latency is mostly attributable to an increase in the time it took to achieve mild pain relief (median, 30 d). This change in latency could reflect the fact that this cohort of patients had a longer duration of follow-up. The latency of pain relief cannot be attributed to radiation doses only. It is true that higher radiation doses achieved better pain relief and that excellent pain relief occurred faster, but the shorter latency to pain relief was not solely the result of higher doses. A quick statistical analysis was performed to compare the Dmax given to the patients with the latency to pain relief of less or more than 2 weeks. Interestingly, the median Dmax doses (73.2 versus 72.9 Gy, $P = 0.9$) were equal in both groups, which demonstrate that there are probably multiple other factors that affect the latency of pain relief, one among many others being the use of 6-MV x-ray beams instead of gamma rays originated from cobalt-60 sources. In comparison with gamma knife and LINAC, however, our latency is still considerably shorter (2, 8, 14, 20, 27, 36).

At a median of 2 years of follow-up, 50% of our patients continued to have excellent pain relief. This is also comparable to other modes of radiosurgery. At gamma knife centers, 40 to 59% sustained pain relief was observed at 2 to 5 years follow-up (14, 20, 22, 27, 36). Although it may not seem as high a rate of pain relief when compared with MVD, we have to remember that MVD provides treatment of the cause of TN in many patients. It is an invasive procedure that is often preferred by younger patients. Our study evaluated only those patients who had contraindications to surgery or who were unwilling to undergo anesthesia and surgery. In addition, 37% of patients had already undergone unsuccessful surgical procedures, including MVD.

We observed that longer treated segments of the nerve ($P = 0.0002$) and higher Dmax and Dmin ($P < 0.00001$) were predictive of a lower recurrence rate. The durability of pain relief was not significantly correlated with sex, age, duration of symptoms, or previous surgical procedures. However, lower posttreatment numbness was predictive of higher pain recurrence rate.

Dose

Animal studies first suggested that cranial nerves could tolerate doses up to 90 Gy before developing axonal necrosis (12). Thus, initial treatments with gamma knife used doses near 90 Gy, and relatively high rates of trigeminal nerve dysfunction were observed (1, 14, 22, 25, 26, 32). Similar observations and complications were observed with LINAC at 90 Gy (8).

We initially treated patients with Dmax near or greater than 80 Gy and observed high rates of numbness with short latencies. Therefore, we titrated both Dmax and Dmin and analyzed radiosurgical treatment parameters with respect to pain relief and side effects. Logistic regression revealed that improved pain relief and a lower recurrence rate was achieved with higher radiation doses. Unfortunately, this was at the expense of increased posttreatment numbness. This encouraged us to look for the optimal treatment parameters, which would prevent bothersome numbness and other complications. We found that the optimal median Dmax dose for the CyberKnife was 78 Gy. It is interesting to note that although a higher Dmax (< 85.4 Gy) was effective and safe in select patients, a lower Dmax (< 70 Gy) either failed to achieve sufficient pain relief or was predictive of higher recurrence rate. In addition, the optimal length of the trigeminal nerve was 6 mm according to our study, which also demonstrated that treatment of segments shorter than 5-mm was not effective. We were impressed with the fact that lower doses were enough to achieve the same efficacy as that achieved with gamma knife. Perhaps this is secondary to the fact that we can deliver a more homogeneous dose, and hence, a higher effective dose to an equivalent length of nerve treated with gamma knife or LINAC.

However, as described in the Results section, higher levels of significance were demonstrated for higher Dmax, higher Dmin, and longer segment of the nerve treated to predict outcome or complications demonstrated compared with the previously defined radiosurgical treatment parameters to predict optimal clinical outcome. This leads us to believe that there may be other factors that influence optimal clinical outcomes, e.g., the radiation dose delivered to the root entry zone or targeting accuracy.

Target

The optimal position along the trigeminal nerve and the length of the nerve treated remain to be defined (8, 19, 22, 36). Kondziolka et al. (16) first suggested placing the isocenter 2 to 3 mm anterior to the dorsal root entry zone and reported only a 10% numbness rate. This is a point on the nerve where the nerve transitions from the peripheral to the central. Goss et al. (8) then suggested including the brainstem in the 50% isodose line to further improve efficacy. However, this led to higher rates of numbness. We have chosen the point suggested by Kondziolka et al. (16) with the hope of comparable numbness rates based on the premise that using CT cisternography rather than MRI for planning would improve accuracy. CT cisternography permits distortion-free visualization of the compressive vessel and the motor root of the trigeminal nerve that can be

easily identified in most cases (31). The main shortcoming of this procedure is the fact that it requires an invasive procedure and is not free of side effects (1% in the current study).

We also examined the impact of the length of the irradiated nerve on clinical outcome. In their randomized trial, Flickinger et al. (7) concluded that treating a longer length of the nerve resulted in a higher rate of complications with no difference in efficacy. The current experience contradicts this conclusion. Although a higher complication rate was observed with the longer segment of lesioned nerve, we also observed significantly greater pain relief. Our original thinking was that irradiating a longer segment of the nerve would lead to improved pain relief outcomes. This could be done in a homogenous way thanks to the nonisocentric inverse planning technique we used. Irradiating up to 12 mm of the nerve provided very fast pain relief but was also associated with a high rate of numbness. Therefore, we reduced the length of the irradiated nerve to 6 mm, with a much lower rate of numbness as a result.

Side Effects and Complications

The most common side effect after radiosurgery is hypesthesia (27, 28). Numbness has been reported to occur in 6 to 54% of patients treated with gamma knife and LINAC (7, 20, 23, 26, 27, 33, 36, 37). Our previous study reported a 51.2% increase of new hypesthesia symptoms (18). In the follow-up study, we observed numbness in 47% of the patients, the majority of whom reported mild to moderate numbness. The median time to the onset of numbness was 6 months (range, 1–14 mo).

As we mentioned previously, Flickinger et al.'s (7) prospective trial suggested that treating longer lengths of the nerve resulted in higher complication rates without improving pain relief. Their technique of placing two 4-mm isocenters next to each would have irradiated extremely long nerve segments (more than 8 mm), which would be comparable to our group of patients with the longest irradiated nerves. However, others have argued that treating longer lengths could improve efficacy without significant complications (1). Given the accuracy of the CyberKnife and ability of the CyberKnife to deliver a nonisocentric homogeneous dose of radiation, we thought treating a longer length of the nerve would improve efficacy; however, we also found that treating a longer length of the nerve and using higher Dmin and Dmax values correlated with numbness ($P < 0.00001$). We have since modified our protocol to treat a 6-mm length of the nerve, which resulted in only a 17% rate of numbness and 3.3% complication rate (decreased corneal reflexes) in the last 30 patients treated. There is definitely a learning curve associated with this novel technology that needs to be taken into account.

CONCLUSION

This study confirms that CyberKnife is an efficacious mode of treatment for TN in selected patients. Our results demonstrate a clear correlation between efficacy and the length of the trigeminal nerve treated or higher Dmax and Dmin used.

However, treating longer lengths of nerve and using higher radiation doses also result in increased numbness. The present outcomes suggest the following optimal radiosurgical treatment parameters: the median Dmax was 78 Gy (range, 70–85.4 Gy) and the median length of the nerve was 6 mm (range, 5–12 mm).

Disclosure

John R. Adler, M.D., is a consultant for Accuray, Inc.

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COMMENTS

The authors should be commended for compiling data from different centers to learn as much as possible regarding outcomes after CyberKnife (Accuracy, Inc., Sunnyvale, CA) radiosurgery for trigeminal neuralgia. Because techniques, nerve targeting, and dose did differ, pooling of data can be of benefit. Several years ago, there was interest by some of the authors to irradiate a longer nerve segment. This was shown to have a higher risk of facial sensory dysfunction, and that concept is no longer advocated. Indeed, their rate of facial numbness was 47% including two patients with dysesthesias. Previously, we conducted a blinded, randomized trial to evaluate the effect of irradiating a longer nerve segment and found that more nerve led to more numbness but not more relief (1).

Their observed rate of complete pain relief was in line with that of other reports, but I imagine that they also provided benefit to other patients whose conditions improved, but who were not completely pain free. Because these patients had medically refractory trigeminal neuralgia, and other surgical procedures had failed in some of them, the outcome of a patient with significant pain reduction (but perhaps still taking some medication because some of these patients are scared to ever stop taking their medication) should still be considered successful.

As the authors describe, doing CyberKnife, or for that matter, gamma knife or anything else, simply refers to the tool being used. There are many ways to use any device. In this series, the nerve was targeted with computed tomographic (CT) scanning, CT cisternography, or CT-magnetic resonance fusion. A wide range of different nerve lengths were irradiated and at different doses. The frequency of x-ray checks for head movement varied among the users. All neurosurgeons performing radiosurgery should pay close attention to the lessons learned from this and other series that help refine the technique. What may seem to be a good thing may prove incorrect once the data are collected. This report should help to create practice recommendations.

Douglas Kondziolka
Pittsburgh, Pennsylvania

1. Flickinger JC, Pollock BE, Kondziolka D, Phuang LK, Foote R, Stafford S, Lunsford LD: Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective, blinded, randomized study. *Int J Radiat Oncol Biol Phys* 51:449–454, 2001.

Villavicencio et al. describe 95 patients with idiopathic trigeminal neuralgia treated with CyberKnife radiosurgery at several centers. Early on, magnetic resonance imaging targeting was not available, so CT cisternography was used. Actuarial 3-year excellent results were obtained in 50% of patients. Complications, some of them serious, were seen in 18% of patients. Many patients had posttreatment facial numbness (47%), which correlated with better long-term pain relief. The

results reported, including long-term success rates and complications, seem similar to results of radiofrequency lesioning. Radiofrequency lesioning has the advantage of immediate pain relief and lower cost. Microvascular decompression (MVD) is generally reported as having better long-term success (perhaps 70–75%), with minimal facial numbness and a lower overall complication rate. In my opinion, MVD remains the treatment of choice for trigeminal neuralgia. I prefer radiofrequency lesioning for those patients who are not good candidates for MVD but offer radiosurgery to those who wish to try to avoid facial numbness.

The authors are to be congratulated on the use of actuarial pain relief statistics and for using the same definition of excellent outcome that is used in surgical reports: no pain and no medications.

William A. Friedman
Gainesville, Florida

This multicenter, retrospective review of CyberKnife radiosurgery for patients with idiopathic trigeminal neuralgia provides valuable information to anyone (physician or patient) considering this approach. In summary, the authors have demonstrated that there are more similarities than differences if one compares their results with those for the published studies on gamma knife (Elekta Instruments, Norcross, GA) radiosurgery for trigeminal neuralgia. First, the chance of being pain-free with medications is nearly identical with approximately 50% of patients having and maintaining this degree of facial pain relief 2 to 3 years after the procedure. Second, higher doses and longer nerve segment irradiation correlate with new trigeminal dysfunction. Third, new facial sensory disturbances are correlated with better facial pain outcomes. I personally question the validity of the observed shortened latency to pain relief (7–14 days) purported by the authors as an advantage of their technique compared with that in other studies (14–28 days). Patients' recollection of precise details is notoriously unreliable, especially when some patients underwent radiosurgery more than 5 years ago. As to the benefit of being "frameless," it is probably up to the individual patient to determine which is more invasive, the placement of a stereotactic head frame or a lumbar puncture to allow a CT cisternogram for stereotactic targeting. Radiosurgery, when performed at centers in which measures have been taken to ensure accurate stereotactic imaging and current dosing guidelines are used, is clearly a safe and reasonable option for patients with trigeminal neuralgia whose pain is not debilitating on a day-to-day basis.

Bruce E. Pollock
Rochester, Minnesota

In this multicenter observational study, Villavicencio et al. present both outcomes and complications in a large series of patients treated for trigeminal neuralgia with CyberKnife radiosurgery. Of these 95 patients followed for a median period of 2 years, approximately 50% had sustained, excellent relief of pain. This result is comparable to that of other radiosurgical series using the more traditional method of frame-based gamma knife irradiation. The complications of treatment—sensory loss, dysesthesias, dry eye, anesthesia dolorosa, and corticospinal injury—have also been reported in other radiosurgical series. Given the limitations of a retrospective study, the authors of this study should be commended for the completeness of their follow-up and listing of complications.

In a continuing effort to make surgery less surgical, stereotactic radiosurgery is now increasingly "frameless," and patients can be treated without the need for either a knife or a needle. Once a radical

concept, the gamma knife has gradually gained mainstream acceptance in the treatment of trigeminal neuralgia and is currently offered alongside more established therapies such as percutaneous ablative procedures and MVD. And just as use of the gamma knife begins to take hold in the armamentarium of treatments for trigeminal neuralgia, along comes the linear accelerator and challenges the conventional wisdom that the tolerance requirements of this target necessitate a fixed radiation source treatment such as the gamma knife. Obviating the need for stereotactic frame placement, the CyberKnife makes treatment seemingly even less invasive. If the results of CyberKnife treatment are comparable to those for the gamma knife series, as this study suggests, then the array of available treatments for trigeminal neuralgia is expanded even further. This expansion is clearly to the benefit of our patients, but only if we continue to critically study the risks and limitations of each available option. With respect to radiosurgery, the current series points out one issue quite clearly: the risks of radiosurgery are not negligible. In this group of patients, treated by three experienced groups, nearly half had a significant sensory deficit. Moreover, both pain relief and sensory deficit increased in incidence with increasing radiation dose. In other words, radiosurgery does not side-step the tendency of ablative surgery to improve outcome at the expense of greater deafferentation.

The treatment of trigeminal neuralgia is likely to continue to improve as technology allows us greater access to the trigeminal nerve with lower morbidity. It is clear that stereotactic radiation has added a valuable option to patients who cannot undergo open or percutaneous surgery. The CyberKnife is simply an extension of this move to make treatments less invasive or uncomfortable. Caution should be exercised here, however. Less discomfort does not necessarily mean better or safer. All surgical treatments for trigeminal neuralgia should ultimately be compared with the gold standards established by MVD and percutaneous ablative procedures over many decades of experience.

Oren Sagher
Ann Arbor, Michigan

Radiosurgery has become one of the cornerstone methods for treatment of trigeminal neuralgia. Numerous publications have documented its superb margin of safety along with clinical results, which have been gratifying to both patients and treating surgeons.

Because this technique was pioneered by gamma knife centers, the method for treatment has traditionally been the use of a single spheroidal "shot" of 70 to 90 Gy delivered via 4-mm collimators to a point on the trigeminal nerve within the prepontine cistern. This method constitutes a radiosurgery retrogasserian rhizolysis. This traditional method has the notable characteristics of very low trigeminal sensory complications

compared with other destructive procedures such as percutaneous lesioning techniques. Median time to relief is generally about 1 month and roughly 80 to 90% of patients can have very satisfactory improvement in pain control. The procedure can be easily repeated with results generally comparable to first-time treatments.

As with any surgical method, however, there is the constant search for improvement in outcomes. Past investigations using the gamma knife device have typically centered on location of shot placement, number of isocenters, and dose. Most centers have continued to use the single-shot method because of treatment time considerations. Subtle differences in dose and shot placement preferences exist, and the ideal combination of these factors continues to be driven by surgeon preference in regard to rates of complications and durability of pain relief. This article demonstrates that to achieve better pain relief in trigeminal radiosurgery treatments, higher complication rates are to be expected. By using larger collimators and treating longer lengths of nerve, the authors have demonstrated shorter latent intervals to pain relief but much higher rates of facial numbness. It is likely that in addition to the increased incidence of facial numbness, the severity of hypoesthesia in some patients was significant, given that two patients developed anesthesia dolorosa. It would appear that a simple relationship familiar to those who have experience with older methods such as percutaneous radiofrequency lesioning continues to hold: more destruction of the nerve results in a greater likelihood of long-term pain relief but with greater hypoesthetic complications.

More concerning, a surprising number of patients suffered significant complications involving hearing, masticatory weakness, foot paresis, and diplopia. Such complications are rare either in the gamma knife or gantry-based LINAC experience. The authors note that they have since changed their methods of treatment planning to irradiate shorter lengths of nerve, resulting in lower complication rates, but it is likely that such changes would also affect overall latency to relief and potentially change the overall likelihood of pain-free outcomes. In fact, it is likely that the use of such modified "non-isocentric" methods may yield outcomes similar to those described with the more traditional shot approach.

Aside from the dose-planning methods, some comment must be made on the use of image-guided radiosurgery. A number of investigators using various implementations have demonstrated that under ideal conditions, image-guided radiosurgery methods can result in accuracy matching that with frame-based methods. It would appear then, that the high complication rates seen in this report are largely the result of choices made in dose planning rather than on issues related to targeting error per se.

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