OBJECTIVE: Although stereotactic radiosurgery is an established procedure for treating trigeminal neuralgia (TN), the likelihood of a prompt and durable complete response is not assured. Moreover, the incidence of facial numbness remains a challenge. To address these limitations, a new, more anatomic radiosurgical procedure was developed that uses the CyberKnife (Accuray, Inc., Sunnyvale, CA) to lesion an elongated segment of the retrogasserian cisternal portion of the trigeminal sensory root. Because the initial experience with this approach resulted in an unacceptably high incidence of facial numbness, a gradual dose and volume de-escalation was performed over several years. In this single-institution prospective study, we evaluated clinical outcomes in a group of TN patients who underwent lesioning with seemingly optimized nonisocentric radiosurgical parameters.

METHODS: Forty-six patients with intractable idiopathic TN were treated between January 2005 and June 2007. Eligible patients were either poor surgical candidates or had failed previous microvascular decompression or destructive procedures. During a single radiosurgical session, a 6-mm segment of the affected nerve was treated with a mean marginal prescription dose of 58.3 Gy and a mean maximal dose of 73.5 Gy. Monthly neurosurgical follow-up was performed until the patient became pain-free. Longer-term follow-up was performed both in the clinic and over the telephone. Outcomes were graded as excellent (pain-free and off medication), good (>90% improvement while still on medication), fair (50–90% improvement), or poor (no change or worse). Facial numbness was assessed using the Barrow Neurological Institute Facial Numbness Scale score.

RESULTS: Symptoms disappeared completely in 39 patients (85%) after a mean latency of 5.2 weeks. In most of these patients, pain relief began within the first week. TN recurred in a single patient after a pain-free interval of 7 months; all symptoms abated after a second radiosurgical procedure. Four additional patients underwent a repeat rhizotomy after failing to respond adequately to the first operation. After a mean follow-up period of 14.7 months, patient-reported outcomes were excellent in 33 patients (72%), good in 11 patients (24%), and poor/no improvement in 2 patients (4%). Significant ipsilateral facial numbness (Grade III on the Barrow Neurological Institute Scale) was reported in 7 patients (15%).

CONCLUSION: Optimized nonisocentric CyberKnife parameters for TN treatment resulted in high rates of pain relief and a more acceptable incidence of facial numbness than reported previously. Longer follow-up periods will be required to establish whether or not the durability of symptom relief after lesioning an elongated segment of the trigeminal root is superior to isocentric radiosurgical rhizotomy.

KEY WORDS: CyberKnife, Nonisocentric, Radiosurgery, Rhizotomy, Trigeminal neuralgia

ABBREVIATIONS: BNI, Barrow Neurological Institute; CT, computed tomographic; Dmax, maximal dose; MRI, magnetic resonance imaging; TN, trigeminal neuralgia
Since January 2005, appropriately selected TN patients at Stanford University Medical Center have been managed with a relatively consistent radiosurgical lesion. In this study, we analyze the outcomes in this cohort of patients and compare them with outcomes in published radiosurgery series.

**PATIENTS AND METHODS**

**Patients**

Patient data were reviewed under an Institutional Review Board-approved protocol. All cases had idiopathic TN of several years’ duration; either pain symptoms were refractory to standard anticonvulsants or the patient experienced severe drug-induced side effects. Cases involving either multiple sclerosis or tumors were excluded from this analysis, as was any patient with atypical facial pain. A total of 46 consecutive TN patients who met these criteria underwent lesioning at Stanford University Medical Center by CyberKnife rhizotomy between January 2005 and June 2007 (Table 1). In this group were 17 men and 29 women with a median age of 78 years (range, 40–94 years). The average time from the earliest onset of TN symptoms to stereotactic radiosurgery was 8.6 years (range, 8 months–20 years). Eleven patients (24%) had failed previous surgical procedures (averaging 1.8 procedures per patient) directed toward their trigeminal symptoms; previous procedures included microvascular decompression (14 patients) and rhizotomy by means of an open (3 patients), glycerol (5 patients), or gamma knife (3 patients) technique. Eleven patients (24%) reported either a moderate or significant degree of facial numbness before CyberKnife rhizotomy, which, unfortunately, was not prospectively scored on the Barrow Neurological Institute (BNI) Scale.

**Radiosurgical Procedure**

Radiosurgical trigeminal rhizotomy was performed with the CyberKnife radiosurgical system, using the technique reported previ-...
follow-up occurred at monthly intervals to ensure a stable clinical status. Any relapse of pain or the development of facial numbness was clinically re-evaluated in person. At each point of contact, patients were grouped into 1 of 4 categories: excellent (pain-free and off medication), good (>90% improvement while still on medication), fair (50–90% improvement), or poor (no change or worsening pain). The presence and timing of facial numbness were also recorded and classified according to the BNI Facial Numbness Scale score (Table 2) (19). Five patients (11%) underwent repeat CyberKnife rhizotomy more than 6 months after the initial procedure. In 4 of these cases, there was inadequate clinical response to the first radiosurgical procedure, whereas in 1 patient there was a relapse in TN symptoms 5 months after the initial operation. Longer-term follow-up was done by mail and telephone. Follow-up data were maintained in a prospective database approved by the Stanford Institutional Review Board.

RESULTS

Thirty-nine patients (85%) in this study had complete disappearance of their TN and were off medications at some point over the course of follow-up. At a mean follow-up duration of 14.7 months (range, 6–29 months; median, 10.5 months), 34 patients (72%) graded their pain relief as excellent, and 11 (24%) described it as good. Consequently, 96% of patients obtained meaningful relief of TN symptoms after CyberKnife rhizotomy. Within this group were 4 patients whose TN did not improve and 1 patient who, at 7 months, experienced recurrent pain. All of these patients were re-treated, and the eventual outcome for these 5 salvage cases was generally excellent (2 patients) or good (2 patients). However, 1 of the 5 re-treated patients had a poor outcome. Although, across the entire series, an improvement in symptoms was typically experienced within a few days or weeks of radiosurgery, the full benefits were obtained after a mean latency of 5.2 weeks (ranging from immediately to 6 months after the procedure).

TN recurred in only a single patient, 7 months after radiosurgery; 9 months after the first procedure, repeat CyberKnife radiosurgical rhizotomy rendered this patient pain-free. At the time of the last follow-up evaluation, 11 patients (24%) reported a significant improvement (3 patients) or even complete abatement (8 patients) in TN symptoms but required, or elected to continue, anticonvulsants for controlling their pain; 3 patients refused to give up their medication only because of concern that their pain might return. Meanwhile, after rhizotomy, TN symptoms were deemed to be worse in only 1 case.

Among the 41 patients who had only a single radiosurgical rhizotomy, significant new ipsilateral facial numbness was reported in 7 cases (17%). New-onset sensory loss typically involved the hemiface and occurred an average of 7 months after the procedure. Interestingly, only 1 of 5 patients who underwent repeat radiosurgery (after a previous gamma knife or CyberKnife rhizotomy) developed significant subsequent facial numbness. At the time of the most recent follow-up evaluation, facial sensation and dysesthesia were categorized in all patients according to BNI Scale score as follows: BNI I, 28 patients; BNI II, 11 patients; and BNI III,
7 patients (Table 2). Three of the 7 patients who reported somewhat bothersome facial numbness treated these symptoms with either neurontin (2 patients) or amitriptyline. It is important to note that 11 patients had some measure of numbness before CyberKnife rhizotomy, and at the time of the last follow-up evaluation, there were no cases of anesthesia dolorosa.

Twenty-eight patients (61%) reported the optimal result of being pain-free and off anticonvulsants, while retaining pre-treatment facial sensation. Six additional patients were pain-free but either elected to remain on reduced doses of anticonvulsants or were unable to taper off such drugs completely without experiencing some recurrent symptoms. Consequently, CyberKnife rhizotomy resulted in 74% of all patients experiencing good to excellent pain relief without significant facial numbness. If one includes 9 additional patients who developed significant facial numbness, 96% of all patients experiencing complete or near-complete relief of trigeminal neuralgia. It is especially noteworthy that among the 31 TN patients who had never undergone any previous surgical procedure, 100% had either a good or excellent response to CyberKnife rhizotomy.
DISCUSSION

The benefits of radiosurgical rhizotomy for TN using the standard isocentric technique are, for many patients, insufficient. Because of the latency of pain relief, overall rate of response, and recurrence of TN symptoms, radiosurgical rhizotomy has limited appeal in the eyes of some neurosurgeons. In an attempt to address the shortcomings of the standard isocentric technique, our group has sought, over several years, to refine a procedure that uses nonisocentric radiosurgery to lesion an elongated segment of the retrogasserian portion of the trigeminal sensory root. Over time, treatment parameters have been optimized to enhance the pain response and reduce facial numbness. The primary objective of the current prospective single-institution study was to characterize short-term outcomes with this technique.

The overall response rate observed in the current CyberKnife series appears satisfactory. In fact, 100% of the patients who had not previously undergone a surgical procedure reported their outcome as either good (13%) or excellent (87%); 1 of these patients needed to be treated twice to achieve this outcome. It is reasonable to propose that this high rate of response is attributable, at least in part, to the longer length of trigeminal nerve lesioned with the CyberKnife.

Although the methods used to score the response of TN to trigeminal rhizotomy are relatively consistent among most clinical series, patient inclusion criteria, length of follow-up, and measures of facial numbness and/or dysesthesia vary widely. Consequently, it is difficult to directly compare those outcomes with those in the current study, and as a result, it cannot be determined at present whether or not irradiating a longer nerve segment is clinically beneficial. Nevertheless, crude comparisons with published radiosurgical rhizotomy series that have used isocentric gamma knife (16, 18) and linear accelerator-based (21) procedures suggest that the outcome with nonisocentric radiosurgical rhizotomy is at least competitive in terms of overall rate of response. Ideally, the current experience could provide a reasonable substrate for a randomized trial that compares the 2 procedures.

The rate of numbness observed in the present series appears to be greater than first reported by several groups using an isocentric gamma knife technique (12, 17, 19). However, higher rates of facial numbness after gamma knife rhizotomy have also been reported, especially with larger and more effective dosing regimens (14, 16). Consequently, the overall incidence and characteristics of sensory loss experienced by some of the patients in the current CyberKnife study seem comparable to what has been reported previously with more conventional isocentric procedures.

Although there are important technical differences, the relatively unremarkable incidence of facial sensory changes that we observed in the present series may challenge one of the key findings reported by Flickinger et al. (6). This randomized trial, which examined the usefulness of 2 adjacent 4-mm gamma knife shots when lesioning the trigeminal nerve, needed to be terminated prematurely when patients in the experimental arm developed severe dysesthesias. The investigators concluded that a longer radiosurgical lesion merely increased the likelihood of "complications" without altering the pain response. What remains unclear is why Flickinger et al. did not encounter an increased rate of response among patients treated with a longer lesion of the trigeminal sensory root. The failure to find such a response would appear to run counter to the experience described by our group (10, 23) and, perhaps, the reports of other gamma knife series that found a direct correlation between integral dose to the trigeminal nerve and the likelihood of pain relief (16). Moreover, the findings of Flickinger et al. (6) would seem to be at odds with the widely observed dose-volume-response phenomenon seen throughout most of radiosurgery. Of note, the Flickinger et al. study compared the standard 1-isocenter treatment with a solitary experimental group in which the longer rhizotomy consisted of 2 adjacent isocenters. By comparison, our group required several years to slowly titrate a radiosurgical dose and volume for lesioning the trigeminal nerve, which is proving, in our experience, to be more optimal in terms of pain relief and avoidance of facial numbness. Perhaps a wider investigation of volumes and doses delivered with a 2-isocenter gamma knife technique might reveal a combination that improves pain relief without further risk of unpleasant facial numbness. Only further study, and most probably a randomized trial, can determine whether or not a longer trigeminal rhizotomy ultimately has any clinical advantages.

One of the primary rationales for modifying the standard radiosurgical rhizotomy technique was to increase the durability of pain relief. Because only 1 of 39 patients experienced a relapse in their TN (7 months after stereotactic radiosurgery), the current experience is encouraging. Nevertheless, much longer follow-up periods will be required to prove that lesioning a longer segment of nerve can significantly increase the durability of the radiosurgical rhizotomy.
There are significant differences between the treatment planning parameters used throughout the current series and those that have been reported in previous descriptions of CyberKnife nonisocentric rhizotomy (23). In the study by Villavicencio et al. (23), the length of lesioned nerve ranged from 3 to 12 mm, whereas the marginal prescription ranged from 40 to 70 Gy and the Dmax ranged from 50 to 86.4 Gy. Moreover, the dose at the edge of the brainstem was as high as 50% in that study. These values contrast markedly with the more uniform 6-mm length of lesioned nerve used throughout the current investigation. Meanwhile, the mean marginal prescription dose that we now report ranged only between 56 and 62 Gy, and the Dmax ranged between 71.4 and 86 Gy. Of note, there was only a single patient who received a dose of 86 Gy, and the next highest Dmax was 77 Gy. Finally, in the present series, we kept the dose at the edge of the brainstem to less than 30% of Dmax. These sizeable differences in treatment planning parameters relative to the series reported by Villavicencio et al. (23) would seem to be responsible for the seemingly better outcome we now report.

Unlike the more defined and reproducible isocentric lesion made with the gamma knife, treatment planning for CyberKnife trigeminal rhizotomy introduces a number of novel yet highly critical treatment planning variables. As a consequence, treatment planning techniques have evolved with ever greater experience, and as a result, the procedure (and dosimetry) used in the current investigation represents an improvement over what was described in the study by Villavicencio et al. (23). Some of the specific treatment planning tactics used in the current series are described previously in Methods. In addition to designing better treatment plans, surgical experience has also been important in better defining the targeted nerve segment. With imaging, the relevant anatomy can be ambiguous in some TN patients, especially after a failed microvascular decompression. Given all of the above factors, improved surgical technique may have been yet another factor in the somewhat different outcome being reported here relative to that of Villavicencio et al. (23).

The incidence and intensity of delayed numbness observed in the current series represents a substantial improvement over what was previously reported for CyberKnife rhizotomy (11, 23). For example, the 17% rate of bothersome facial numbness (BNI III) that we describe in the current report is a significantly lower rate than the 28% observed by Villavicencio et al. (23), which also included BNI scores of III (16%) and IV (12%). In addition, none of the patients in the current series developed other, even more serious complications such as anesthesia dolorosa, trismus, masticator weakness, diplopia, decreased hearing, dry eye syndrome, or paresis, all of which were described by Villavicencio et al. As a consequence, it appears that the dose-volume parameters being used with the present nonisocentric technique make for a better clinical outcome. Given the reported latency between radiosurgery and the onset of facial numbness, it is quite possible that, with further follow-up, additional patients will develop sensory symptoms. However, because the mean overall follow-up duration is 14.7 months in the present study, whereas the mean time to occurrence of numbness is 7 months, it seems unlikely that loss of facial sensation will occur in enough additional patients to alter this primary finding. Ultimately, it seems clear that numbness is significantly less likely using the optimized treatment parameters of the present study than it was during the developmental stages of CyberKnife rhizotomy for TN.

The specific treatment parameters used in the current series to achieve a lower complication rate thus far do not appear to have compromised the short-term efficacy of radiosurgical rhizotomy when a comparison is made to the Villavicencio et al. series (23). The 72% rate of being pain-free and off medication that is observed in the current investigation compares favorably with the 67% rate of excellent outcome described in the earlier study. Although the longer-term likelihood of TN recurrence when both the length of nerve and dose have been optimized remains unknown, the preliminary 2% rate of relapse we observe in the current study seems competitive with the 37% rate of recurrent TN noted by Villavicencio et al., albeit the follow-up period for their study is longer, at 2 years. Clearly, additional follow-up is needed to compare the ultimate durability of these 2 procedures.

It is worth pointing out that TN is somewhat unique among pain syndromes in that pain is usually either present or absent. As a consequence, the large majority of patients with complete relief were easy to categorize as such. In contrast, the nature of symptoms and outcome among patients with only partial pain relief was more complex and less conducive to the relatively simplistic measuring tools used in this investigation. Moreover, several of the patients in this series had coexisting facial pain syndromes that were not TN-like and were precipitated in part by previous failed ablative procedures or microvascular decompression. Because some of these same patients also eventually developed post-rhizotomy delayed facial numbness, it was often difficult to distinguish new sensory symptoms from their preexisting pain condition. Therefore, one of the limitations of the current investigation is that, unlike the recent study by Régis et al. (18), there is not a more detailed analysis of our patients’ ultimate facial sensation. Despite this shortcoming, the current investigation should provide a useful starting point for future investigation.

The biological mechanism underlying the cessation of TN symptoms after radiosurgical rhizotomy remains poorly defined. Some investigators have concluded that the likelihood of a clinical response to radiosurgery correlates with the development of facial numbness (16, 19). This suggests that a common mechanism underlies these 2 phenomena. However, their very different time course implies that distinct mechanisms underlie pain relief and facial numbness; TN pain abates relatively rapidly after a radiosurgical rhizotomy, whereas facial numbness is clearly a delayed event (6–9 months or more after radiosurgery). Meanwhile, both the latency of sensory changes and the appearance of enhancement on contrast MRI at the root entry zone, the latter being consistent with breakdown in the blood-brain barrier, strongly suggest that facial numbness stems from injury to the microvasculature of the trigeminal nerve and adjacent brainstem (7). If so, such a phenomenon raises some intriguing possibilities for intervention. In particu-
lar, the use of an intravascular free radical scavenger, like amifostine (Ethylol; Medimmune, Gaithersburg, MD), at the time of radiosurgery might provide relative radioprotection to the endothelium and limit the incidence of delayed microvascular injury. Theoretically, such an agent would not alter the biological mechanism underlying the therapeutic benefits of radiotherapy. A randomized trial is being planned to investigate such a possibility.

CONCLUSION

Compared with previous reports that describe the clinical outcome after nonisocentric radiosurgical rhizotomy in patients with TN, the present investigation demonstrates both high rates of pain relief and an acceptable incidence of facial numbness. We are not able to determine whether or not this technique can ultimately improve on either the rate of response or the durability of symptom relief that can be achieved with the standard isocentric radiosurgical rhizotomy. Further study is warranted, and, ideally, a randomized trial comparing isocentric and nonisocentric techniques should be conducted.

Disclosure

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