LONG-TERM RESULTS OF RADIOSURGERY FOR REFRACTORY CLUSTER HEADACHE

Shearwood McClelland III, M.D.
Department of Neurosurgery,
University of Minnesota
Medical School,
Minneapolis, Minnesota

Rahul D. Tendulkar, M.D.
Brain Tumor Institute,
Department of Radiation Oncology,
The Cleveland Clinic Foundation,
Cleveland, Ohio

Gene H. Barnett, M.D.
Brain Tumor Institute,
Department of Neurosurgery,
The Cleveland Clinic Foundation,
Cleveland, Ohio

Gennady Neyman, Ph.D.
Brain Tumor Institute,
Department of Radiation Oncology,
The Cleveland Clinic Foundation,
Cleveland, Ohio

John H. Suh, M.D.
Brain Tumor Institute,
Department of Radiation Oncology,
The Cleveland Clinic Foundation,
Cleveland, Ohio

Reprint requests:
John H. Suh, M.D.,
Department of Radiation Oncology,
Desk T28,
The Cleveland Clinic Foundation,
9500 Euclid Avenue,
Cleveland, Ohio 44195.
E-mail: suhj@ccf.org

Received, April 19, 2006.
Accepted, July 29, 2006.

OBJECTIVE: Medically refractory cluster headache (CH) is a debilitating condition for which few surgical modalities have proven effective. Previous reports involving short-term follow-up of CH patients have reported modest degrees of pain relief after radiosurgery of the trigeminal nerve ipsilateral to symptom onset. With the recent success of deep brain stimulation as a surgical modality for these patients, it becomes imperative for the long-term risks and benefits of radiosurgery to be more extensively delineated. To address this issue, we present our findings from the largest retrospective series of patients undergoing radiosurgery for CH with extended follow-up periods.

METHODS: Between 1997 and 2001, 10 patients with CH underwent gamma knife radiosurgery at our institution. All patients fulfilled clinical criteria for treatment, including complete resistance to pharmacotherapy (usually methysergide, verapamil, and lithium), pain primarily localized to the ophthalmic division of the trigeminal nerve, and psychological stability. The mean age at radiosurgery was 40.3 years (range, 26–62 yr), and the average CH duration was 11.3 years (range, 2–21 yr). Patients received 75 Gy to the 100% isodose line delivered to the most proximal part of the trigeminal nerve where the 50% isodose line was outside the brainstem (4-mm collimator), with a mean follow-up period of 39.7 months (range, 5–88 mo). Pain relief was defined as excellent (free of CH with minimal or no medications), good (50% reduction of CH severity and frequency with medications), fair (25% reduction of CH severity and frequency with medications), or poor (less than 25% reduction of CH severity and frequency with medications).

RESULTS: After radiosurgery, pain relief was poor in nine patients and fair in one patient. Six patients with poor to fair relief initially experienced excellent to good relief (range, 2 wk–2 yr after treatment) before regressing. Five patients (50%) experienced trigeminal nerve dysfunction, manifesting predominantly as facial numbness after treatment.

CONCLUSION: Although some patients may experience short-term pain relief, none had relief sustainable for longer than 2 years. The results from this series indicate that radiosurgery of the trigeminal nerve does not provide long-term pain relief for medically refractory CH.

KEY WORDS: Gamma knife radiosurgery, Long-term follow-up, Pain relief, Refractory cluster headache, Trigeminal nerve

Neurosurgery 59:1258–1263, 2006 DOI: 10.1227/01.NEU.0000245614.94108.4B www.neurosurgery-online.com

One of the most debilitating headache syndromes, cluster headache (CH), is characterized by sudden onset of unilateral pain originating around the temple, eye, or cheek, primarily along the ophthalmic division of the trigeminal nerve. The excruciating nature of the pain makes CH a highly disabling disorder, particularly because attacks can last anywhere from minutes to hours, can occur one or multiple times a day, and are often accompanied by signs of autonomic dysfunction (9). The prevalence of CH in the United States is 0.24%, of which 10% of patients develop chronic CH, defined as either pain without remission for more than 1 year or closely spaced attacks with remission periods lasting no longer than 30 days (2, 12). Approximately 20% of chronic CH patients are highly refractory to medical treatment (13). Consequently, multiple surgical modalities have been

attempted to alleviate the severe symptomatology in this patient population. These therapies have included lesioning of the trigeminal nerve, sectioning of the sphenopalatine ganglion, sectioning of the greater superficial petrosal nerve, glycerol injection of Meckel's cave, sectioning of the intermedius nerve, microvascular decompression of the trigeminal nerve or the nervus intermedius, and deep brain stimulation (DBS) of the posterior hypothalamus (4, 8, 14–16, 20, 23, 24, 26, 27). However, each of these modalities involves invasive surgery and/or ablation of nerve structures, both of which are fraught with morbidity, including anesthesia dolorosa, aseptic meningitis, deafness, tinnitus, hyperacusis, paralysis of muscles of facial expression, corneal abrasions, and diplopia (17). To avoid these undesirable complications, stereotactic radiosurgery has been proposed as an alternative modality. Two previous studies have examined gamma knife radiosurgery of the trigeminal nerve for treating refractory CH, reporting relatively contrasting results with short-term follow-up (1, 3). In this study, the largest retrospective series of trigeminal nerve radiosurgery for refractory CH with long-term follow-up, we detail our experience and clinical findings.

TABLE 1. Demographics of patients who underwent radiosurgery for medically refractory cluster headaches[a]

Patient no.	Age at RS (yr)/sex	Side of RS	CH preoperative duration (yr)	Gy delivered	Follow-up (mo)	Morbidity	Pain relief
1	41/M	R	21	75	88	None	Poor
2	32/M	L	8	75	83	None	Poor
3	40/M	R	13	75	5	None	Poor
4	33/M	R	2	75	10	None	Poor
5	34/M	L	6	75	22	L facial numbness	Fair
6	62/M	L	20	75	51	L facial numbness	Poor
7	29/M	L	8	75	52	None	Poor
8	26/M	R	8	75	19	R facial numbness	Poor
9	53/M	R	12	75	27	Unspecified facial numbness	Poor
10	53/M	R	15	75	40	R facial numbness	Poor

[a] RS, radiosurgery; CH, cluster headache; R, right; L, left.

PATIENTS AND METHODS

Between 1997 and 2001, 10 patients with refractory chronic CH were admitted for outpatient radiosurgery to the Cleveland Clinic Health System Gamma Knife Center. Criteria for inclusion were 1) International Headache Society classification of chronic CH and 2) medically refractory to appropriate drug therapy (usually methysergide, lithium, and verapamil) despite high therapeutic serum concentrations. The innovative nature of the procedure was explained to all patients, as were alternative treatments and risks. This retrospective review was approved by our Institutional Review Board.

Patients arrived the morning of the procedure. The stereotactic frame was applied with the patient under local anesthesia and intravenous sedation. The frame was oriented to make the base ring of the frame parallel to the trigeminal nerve axis (22). Preoperative imaging systematically included magnetic resonance imaging (MRI) and computed tomographic scans. Axial MRI scan sequences (Siemens 1.5 T, New York, NY) included T2-weighted high-resolution (0.5 mm) three-dimensional acquisition and three-dimensional T1-weighted acquisition, as previously described (1). Computed tomographic scanning of the bone window served to check and (if necessary) correct for potential MRI scan distortion (1). A single 4-mm collimator was used to target the cisternal segment of the nerve ipsilateral to symptom onset, defined as the portion between Meckel's cave and the pons, with three patients also targeted with an 8-mm collimator (this was part of a prospective trial evaluating concentric
4- and 8-mm collimators). The anatomic target was the most proximal part of the trigeminal nerve where the 50% isodose line was outside the brainstem (anterior cisternal target), previously described as the radiosurgical target for refractory CH (1, 3, 21, 22). All patients received 75 Gy (collimator factor = 0.80, equivalent to 82 Gy with contemporary collimator factor of 0.87) to the 100% isodose line (approximately 10–15 Gy was delivered to the brainstem), using a model B gamma knife (Elekta AB, Stockholm, Sweden), as previously reported for trigeminal neuralgia (11). Both eyes were shielded in all patients.

RESULTS

The mean age of the 10 patients (all men) was 40.3 years (range, 26–62 yr), with the mean duration of CH being 11.3 years (range, 2–21 yr) (*Table 1*). The mean distance from the center of the shot and the emergence of the nerve from the brainstem was 3.9 mm (median, 4.0 mm) (*Table 2*). The mean dose at the emergence of the trigeminal nerve from the brainstem was 32.6 Gy (median, 33.5 Gy), with 52.6% of the nerve receiving at least 50% of the maximal dose, and an average dose of 44 Gy delivered directly to the nerve (*Table 2*). The mean follow-up period was 39.7 months (range, 5–88 mo). Outcomes were divided into four pain relief categories, as previously described (1, 3): excellent, free of CH with minimal or no medications; good, 50% reduction of CH severity and frequency with medications; fair, 25% reduction of CH; and poor, less than 25% reduction of CH. After radiosurgery, pain relief was poor in nine patients and fair in one (*Table 1*). Six patients with poor to fair relief initially expe-

TABLE 2. Details of radiosurgical dosing[a]

Patient no.	Distance from center of shot to the brainstem (mm)	Dose at emergence of CN V from the brainstem (Gy)	Percent volume of CN V receiving >50% of maximal dose (%)	Average dose to CN V (Gy)
1	N/A	N/A	N/A	N/A
2	3.2	35.9	61	50.6
3	5.3	13.8	40	36.5
4	3.6	31.1	59	48.6
5	4	26.3	33	32.7
6	2.8	42.1	47	41.9
7	4.1	23	40	36.3
8	4.5	39.8	55	44.2
9	N/A	N/A	N/A	N/A
10	3.9	48.5	86	61.1
Median	4.0	33.5	51.0	43.1
Mean	3.9	32.6	52.6	44.0
Min	2.8	13.8	33.0	32.7
Max	5.3	48.5	86.0	61.1

[a] CN, cranial nerve; N/A, not available; min, minimum; max, maximum.

rienced excellent to good relief (range, 2 wk–2 yr after treatment) before regressing. Five patients experienced trigeminal nerve dysfunction, manifesting predominantly as facial numbness in the distribution of the trigeminal nerve after treatment (*Table 1*). No patients experienced corneal pathology or anesthesia dolorosa.

DISCUSSION

The concept of radiosurgery for treating refractory CH originated from the observation that invasive surgical approaches involving the trigeminal nerve provided moderate degrees of pain relief for an otherwise untreatable population of patients (4, 8, 10, 14, 15, 16, 20, 23–27). The use of radiosurgery as a treatment for refractory CH via targeting of the trigeminal nerve was first reported by Ford et al. in 1998 (3), whose experience in six refractory CH patients revealed pain relief after radiosurgery within days, with four patients having excellent pain relief, one patient having good pain relief, and one patient having fair relief—all with "negligible short- and long-term sequelae" after 8 to 14 months of follow-up. These positive findings (66% with excellent pain relief; 83% with excellent or good pain relief; and 0% morbidity) served as a foundation for using radiosurgery at our institution for treating refractory CH.

However, a more recent study involving radiosurgery of the trigeminal nerve for refractory CH painted a far less rosy outcome (1). In this report, a prospective open study involving 10 patients, three patients had excellent pain relief, three had good pain relief, and the remaining four had poor pain relief after an average follow-up period of 1 year. These findings (30% excellent pain relief; 60% with excellent or good pain relief) (1) are markedly different from the results of Ford et al. (3), but even more distressing was the incidence of postoperative side effects. Three patients developed paresthesia without hypoesthesia, one developed hypoesthesia, and one developed deafferentation pain debilitating enough to require subsequent cortical stimulation. Although some pain relief was achieved, it was accomplished at a high cost—50% morbidity, which is substantially higher than radiosurgery of the same target for trigeminal neuralgia (7). Of greater concern was that two of the three patients with excellent pain relief had very short follow-up periods (<1 yr) because multiple surgical experiences (including ours) have shown that initial response to treatment may be followed by later recurrence. Therefore, it is likely that the most accurate interpretation of these findings is that radiosurgery for this indication provides a moderate chance of pain relief (40–60% excellent to good), but a significant chance of morbidity (one out of two patients). For this reason, the authors correctly concluded that radiosurgery of the trigeminal nerve for refractory CH may not be warranted, although using the same target for treating other disorders (i.e., trigeminal neuralgia) should not be neglected.

Our findings (90% poor; 10% fair; 0% excellent or good; and 50% morbidity) align more with the negative results of Donnet et al. (1) than the positive report of Ford et al. (*Table 3*) (3). These results are likely because of the significantly longer mean follow-up period of our study compared with the previous studies (*Table 3*). Had our study been conducted using similar follow-up periods to the previous studies, two of our patients who ultimately had a poor outcome would have been labeled as having excellent pain relief because their relief did not regress until more than 18 months after treatment. This is an important factor to consider in evaluating radiosurgery as a modality for treating this condition; even patients with excellent outcomes initially do not have sustainable results over time. Furthermore, the 50% morbidity in our series, although not as severe as that presented by Donnet et al. (1), underscores the point that radiosurgery is not without risk and should not be approached casually by either the patient or the treating physician (*Table 3*). Despite the 20% short-term pain relief witnessed in our series, the 0% long-term pain relief combined with the 50% morbidity rate leads us to strongly doubt the efficacy of radiosurgery for refractory CH.

The lack of long-term efficacy demonstrated by our results is not surprising; multiple neuroimaging studies have suggested that the pathophysiological mechanism underlying CH is not peripheral, but rather central, in origin, because hypothalamic

TABLE 3. Literature review of radiosurgery for medically refractory cluster headache

Series (ref. no.)	No. of patients	Maximum dose used	Mean follow-up (mo)	Excellent relief	Good relief	Fair relief	Poor relief	Morbidity (% of patients)
Ford et al., 1998 (3)	6	70 Gy	11.7	4 (66.7%)	1 (16.7%)	1 (16.7%)	0 (0%)	1 paresthesia of eyebrow; 1 transient tingling of face (33.3%)
Donnet et al., 2005 (1)	10	80–85 Gy	13.2	3 (30%)	3 (30%)	0 (0%)	4 (40%)	3 paresthesia without hypoesthesia; 1 hypoesthesia; 1 deafferentation pain (50%)
Present study	10	75 Gy	39.7	0 (0%)	0 (0%)	1 (10%)	9 (90%)	5 facial numbness (50%)

hyperactivity may be linked to CH attacks (5, 19). Additionally, positron emission tomography scanning has recently revealed activation in the ipsilateral posteroinferior hypothalamic gray matter during CH attacks, and MRI scan data has demonstrated increased hypothalamic size and neuronal hypothalamic density in patients with CH (6, 18). Consequently, it becomes logical to understand why targeting the trigeminal nerve as a treatment for refractory CH would provide less than adequate pain relief. Additionally, the hypothesis of a central origin of CH attacks provides an explanation regarding why DBS of the posterior hypothalamus has proved so effective both in reducing or eliminating pain in refractory CH patients and in increasing the efficacy of previously ineffective CH medications. These results have remained stable in both the short and long term (4, 14, 15).

The relative failure of trigeminal nerve radiosurgery to provide adequate pain relief in refractory CH lends further support to the hypothesis that CH is central in origin. Because of the marked clinical efficacy of DBS with minimal morbidity in this patient population, radiosurgical treatment of refractory CH may have to involve a central target to provide the possibility of achieving benefits comparable to DBS. However, because of the permanence and irreversibility of a radiosurgical lesion compared with the adjustability and reversibility of DBS, the future of radiosurgery for the treatment of refractory CH seems limited. Furthermore, our long-term findings concur with those of a recently concluded prospective trial involving this patient population (J Regis, personal communication, 2006). Although the use of combined trigeminal and sphenopalatine ganglion radiosurgery to impact afferent and efferent fibers has been anecdotally suggested, the results of this modality for refractory CH have yet to be reported.

CONCLUSION

In the largest retrospective series on radiosurgery for refractory CH with extended patient follow-up, we found that radiosurgery of the trigeminal nerve does not provide adequate long-term pain relief for medically refractory CH. Furthermore, radiosurgery for this condition involves substantial morbidity. Given the success of DBS for treating this patient population, future radiosurgical endeavors may require the choice of a different anatomic target. Based on our results, we do not recommend the use of radiosurgery to the proximal trigeminal nerve.

REFERENCES

1. Donnet A, Valade D, Regis J: Gamma knife treatment for refractory cluster headache: Prospective open trial. **J Neurol Neurosurg Psychiatry** 76:218–221, 2005.
2. Dousset V, Henry P, Michel P: Epidemiology of headache. **Rev Neurol** (Paris) 156 [Suppl 4]:S24–S29, 2000.
3. Ford RG, Ford KT, Swaid S, Young P, Jennelle R: Gamma knife treatment of refractory cluster headache. **Headache** 38:3–9, 1998.
4. Franzini A, Ferroli P, Leone M, Broggi G: Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: First reported series. **Neurosurgery** 52:1095–1101, 2003.
5. Goadsby PJ, Bahra A, May A: Mechanisms of cluster headache. **Cephalalgia** 19 [Suppl 23]:19–23, 1999.
6. Goadsby PJ, May A: PET demonstration of hypothalamic activation in cluster headache. **Neurology** 52:1522, 1999.
7. Goss BW, Frighetto L, DeSalles AA, Smith Z, Solberg T, Selch M: Linear accelerator radiosurgery using 90 gray for essential trigeminal neuralgia: Results and dose volume histogram analysis. **Neurosurgery** 53:823–830, 2003.
8. Greene MW: Long-term follow-up of chronic cluster headache treated surgically with trigeminal tractotomy. **Headache** 43:479–481, 2003.
9. Headache Classification Subcommittee of the HIS: International classification of headache disorders, 2nd ed. **Cephalalgia** 24 [Suppl 1]:9–160, 2004.
10. Kirkpatrick PJ, O'Brien MD, MacCabe JJ: Trigeminal nerve section for chronic migrainous neuralgia. **Br J Neurosurg** 7:483–490, 1993.
11. Kondziolka D, Lunsford LD, Flickinger JC, Young RF, Vermeulen S, Duma CM, Jacques DB, Rand RW, Regis J, Peragut JC, Manera L, Epstein MH, Lindquist C: Stereotactic radiosurgery for trigeminal neuralgia: A multiinstitutional study using the gamma unit. **J Neurosurg** 84:940–945, 1996.
12. Kudrow L: Diagnosis and treatment of cluster headache. **Med Clin N Am** 75:579–594, 1991.
13. Leone M: Chronic cluster headache: New and emerging treatment options. **Curr Pain Headache Rep** 8:347–352, 2004.
14. Leone M, Franzini A, Broggi G, Bussone G: Hypothalamic deep brain stimulation for intractable chronic cluster headache: A 3-year follow-up. **Neurol Sci** 24 [Suppl 2]:S143–S145, 2003.
15. Leone M, May A, Franzini A, Broggi G, Dodick D, Rapoport A, Goadsby PJ, Schoenen J, Bonavita V, Bussone G: Deep brain stimulation for intractable chronic cluster headache: Proposals for patient selection. **Cephalalgia** 24:934–937, 2004.
16. Matharu MS, Goadsby PJ: Persistence of attacks of cluster headache after trigeminal nerve root section. **Brain** 125:976–984, 2002.
17. Mathew NT, Hurt W: Percutaneous radiofrequency trigeminal gangliorhizolysis in intractable cluster headache. **Headache** 28:328–331, 1988.
18. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, Goadsby PJ: Correlation between structural and functional changes in brain in an idiopathic headache syndrome. **Nat Med** 5:836–838, 1999.
19. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ: Hypothalamic activation in cluster headache attacks. **Lancet** 352:275–278, 1998.
20. Meyer JS, Binns PM, Ericsson AD, Vulpe M: Sphenopalatine gangionectomy for cluster headache. **Arch Otolaryngol** 92:475–484, 1970.
21. Regis J: High-dose trigeminal neuralgia radiosurgery associated with increased risk of trigeminal nerve dysfunction. **Neurosurgery** 50:1401–1403, 2002.

22. Regis J, Bartolomei F, Metellus P, Rey M, Genton P, Dravet C, Bureau M, Semah F, Gastaut JL, Peragut JC, Chauvel P: Radiosurgery for trigeminal neuralgia and epilepsy. **Neurosurg Clin N Am** 10:359–377, 1999.
23. Rowed DW: Chronic cluster headache managed by nervus intermedius section. **Headache** 30:401–406, 1990.
24. Rozen TD: Interventional treatment for cluster headache: A review of the options. **Curr Pain Headache Rep** 6:57–64, 2002.
25. Sanders M, Zuurmond WW: Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: A 12- to 70-month follow-up evaluation. **J Neurosurg** 87:876–880, 1997.
26. Solomon S, Apfelbaum RI: Surgical decompression of the facial nerve in the treatment of chronic cluster headache. **Arch Neurol** 43:479–482, 1986.
27. Taha JM, Tew JM Jr: Long-term results of radiofrequency rhizotomy in the treatment of cluster headache. **Headache** 35:193–196, 1995.

Acknowledgments

We thank Jane Rein and Betty Jamison for their invaluable assistance. None of the authors received any financial support in conjunction with the generation of this article.

COMMENTS

This study deals with a surgical treatment of chronic cluster headache (CCH), that when it becomes drug resistant, is very disabling for the patient and is sometimes life-threatening. The authors present an important contribution showing that new technologies (in this case, radiosurgery), with any type of instrument and with high accuracy of dose planning, does not solve the therapeutic problem. Indeed, it is well known that trigeminal lesioning, in the past, from open to radiofrequency percutaneus rhizotomy could achieve good but transient pain control. Similarly, the sphenopalatine ganglion lesioning produces only short-term success.

Our experience with these failures, as well as the metabolic, positron emission tomographic, and functional magnetic resonance imaging data from May et al. (2), which showed that the "motor" of the disease is central, brought our group to propose deep brain stimulation of the posterior hypothalamus for the treatment of cluster headaches. The long-term follow-up results are more than satisfying (1). The authors should be complimented not only for their ethical honesty in providing us a negative result, relative to the newest methodology of lesioning the trigeminal nerve for achieving pain control, but also for their contribution in radiosurgical methodology, dosimetry, and targeting that are very important in refining this therapeutic tool for different indications.

Giovanni Broggi
Milan, Italy

1. Franzini A, Ferroli P, Leone M, Broggi G: Stimulation of the posterior hypothalamus for the treatment of chronic intractable cluster headache: First reported series. **Neurosurgery** 52:1095–1101, 2003.
2. May A, Bahar A, Buchel C, Frackowiak RS, Goadsby PJ: PET and MRA findings in cluster headache and MRA in experimental pain. **Neurology** 55:1328–1335, 2000.

The authors discuss their results after trigeminal nerve radiosurgery and conclude that this nerve may not be an optimal target for this pain syndrome. However, patients did have short-term benefits. Was this a transient physiological effect mediated via the nerve? Was it a placebo effect? They discuss the role of the hypothalamus and other potential central targets to relieve CCH. Certainly other facial pain syndromes have been improved after periaqueductal gray stimulation, thalamotomy, and motor cortex stimulation. The invasiveness and cost of hypothalamic stimulation for a headache syndrome may sound excessive, but it could be warranted for patients with such severe pain. Our results with CCH radiosurgery have been more encouraging, and we will continue to collect data on these patients. The main observation of this report is that relief is not long lasting. If true, this would certainly limit the role of radiosurgery in this disorder.

Douglas Kondziolka
Pittsburgh, Pennsylvania

McClelland et al. provide us with a very important contribution about the results of radiosurgery in cluster headaches. In 1998, the pionnering work of Ford et al. (3) raised hopes for patients presenting with very severe and drug-resistant cases. This initial report presented radiosurgery in a small group of four patients as a potential safe and effective strategy. No mid- or long-term results of this small group of patients have ever been published by these authors. Unfortunately, in a prospective trial conducted under strict methodological rules, results have turned out to be much less satisfactory (2). Our first alarming, short-term report turned out to be even worse in the long-term (1). The high rate of trigeminal nerve injury is especially intriguing owing to its rarity in patients presenting with "tic douloureux" and treated according to the same protocol or even a higher dosage (4, 5).

Some authors have argued that the important discrepancy between Ford et al.'s series and ours was related to the use of a different target, the dorsal root entry zone in the former and the retrogasserian in the latter. The report from McClelland et al. does not confirm this interpretation. Using the so-called dorsal root entry zone target, they have observed a high rate of toxicity and a low rate of efficacy of radiosurgery in CCH that we have observed using the retrogasserian target. In spite of the use of two very different targets, the results of McClelland et al. and our group are very much in accordance. Thus, we do not recommend radiosurgical treatment of the Vth nerve in CCH.

Anne Donnet
Neurologist
Jean Régis
Marseille, France

1. Donnet A, Tamura M, Valade D, Régis J: Trigeminal nerve radiosurgical treatment in intractable chronic cluster headache: Unexpected high toxicity. **Neurosurgery** 59:1252–1257, 2006.
2. Donnet A, Valade D, Regis J: Gamma knife treatment for refractory cluster headache: prospective open trial. **J Neurol Neurosurg Psychiatry** 76:218–221, 2005.
2. Ford RG, Ford KT, Swaid S, Young P, Jennelle R: Gamma knife treatment of refractory cluster headache. **Headache** 38:3–9, 1998.
3. Massager N, Nissim O, Murata N, Devriendt D, Desmedt F, Vanderlinden B, Regis J, Levivier M: Effect of beam channel plugging on the outcome of gamma knife radiosurgery for trigeminal neuralgia. **Int J Radiat Oncol Biol Phys** 65:1200–1205, 2006.
4. Régis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F: Prospective evaluation of Gamma Knife Radiosurgery in Essential Trigeminal Neuralgia. **J Neurosurg** 104:913–924, 2006.

Browsing through recent issues of *Neurosurgery*, I was not surprised to find that more than 70% of clinical studies that evaluated a specific therapy found a positive outcome for that therapy. This type of publication bias exists throughout the medical literature (3), as does a bias towards only reporting "significant" results (1). It is, there-

fore, relatively unusual to see a well-performed study come down so negatively on a treatment. Using a standard radiosurgical target and comparing their results with previous studies, McClelland et al. found that 90% of patients with cluster headache failed to achieve even 25% reduction in their symptoms, with not a single patient reporting excellent or good results.

This is a carefully done retrospective analysis with a mean follow-up period of more than 3 years and with a maximum follow-up period of more than 7 years. Follow-up periods of this length may, perhaps, unfairly evaluate a therapy, as even our most cherished interventions may eventually be deemed ineffective under the scrutiny of sufficiently long follow-up periods. However, when treating such a debilitating disease as refractory cluster headache, one must ask, how much effect is enough? What length of time is long enough? Six out of 10 patients in this study had excellent to good relief for periods of up to 2 years. Is this worth the 50% rate of facial numbness?

As the authors state, hypothalamic deep brain stimulation has been shown by one group to be an effective treatment for refractory cluster headaches (2). Unlike radiosurgery, this modality is certainly more invasive and carries the risk of serious hemorrhage or even death. Studies are now underway to attempt to replicate the remarkable positive results reported in early series. Only time will tell if the natural tendency of follow-up studies to contradict initial laudatory and often-cited studies (4) will dampen enthusiasm for deep brain stimulation for cluster headaches.

Jaimie M. Henderson
Stanford, California

1. Dickersin K: The existence of publication bias and risk factors for its occurrence. **JAMA** 263:1385–1389, 1990.
2. Franzini A, Ferroli P, Leone M, Broggi G: Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. **Neurosurgery** 52:1095–1101, 2003.
3. Gluud LL: Bias in clinical intervention research. **Am J Epidemiol** 163:493–501, 2006.
4. Ionnidis JP: Contradicted and initially stronger effects in highly cited clinical research. **JAMA** 294:218–228, 2005.

This study outlines and further defines the results, poor as they may be, of stereotactic radiosurgery in the treatment of cluster headaches. The authors join a growing group of investigators who report unexpectedly poor outcomes after irradiation of the trigeminal nerve in the treatment of cluster headaches. Given the fact that stereotactic radiosurgery has been used with some measure of success in the treatment of trigeminal neuralgia, series such as this one raise the question of what makes this particular condition so different. Is it possible that the trigeminal nerve is the wrong target in cluster headache? Is it, perhaps, that the trigeminal nerve is more sensitive to radiation in a condition such as cluster headache? These are questions on which one can only speculate. The only clear message of this study is to those who advocate stereotactic radiosurgery as a minimally invasive procedure. The radiobiology of focused radiation is not delineated well enough, and the physiological effects of various brain structures are not uniform enough to justify the enthusiasm currently enjoyed by this therapeutic modality.

Oren Sagher
Ann Arbor, Michigan

Sistine Chapel Ceiling (1508–12): Detail of the hands of God and Adam, (fresco) (post restoration) by Michelangelo Buonarroti (1475–1564) Vatican Museums and Galleries, Vatican City.