Clustering headache is a relatively rare periodic headache and facial pain syndrome that may persist for weeks or even months. Cluster headaches occur in 0.4% of the male population and < 0.08% of the female population. Approximately 90% of patients with CH have an episodic disorder, while 10% have chronic CH. Chronic CH attacks vary, from closely spaced pain with remissions lasting no longer than 30 days, to continuous pain without remission lasting more than a year. In contrast, episodic CHs are characterized by 1–3 attacks of peri-orbital pain per day over a 6–12-week period, followed by an average pain-free interval of 6 months to 1 year, or even remissions lasting years. Cluster headache may be associated with autonomic symptoms including ipsilateral lacrimation, conjunctival injection, nasal congestion, rhinorrhea, sweating, pallor, and Horner syndrome.
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imately 20% of patients with chronic CH are refractory to medically treatment.14 Thus, multiple surgical procedures for CH have been proposed. Gasserian ganglion alcohol injections, TN root sectioning,9,10,18 glycerol rhizotomy,29 MVD of the TN with or without sectioning of the nervus intermedius,30 and DBS of the posterior hypothalamus8,15,16 have been performed. Destructive procedures of the TN may lead to facial sensory loss even to the level of anesthesia dolorosa. More invasive procedures may be associated with meningitis, hearing impairment, facial weakness, keratitis, and diploria.19

Stereotactic radiosurgery has been proposed as a minimally invasive alternative management option for CH.4,5,13,21 The NAGKC was established to evaluate outcomes of selected clinical indications that are relatively rare (such as CH) and to facilitate prospective clinical trials. This first report is based on retrospective data provided by 4 academic medical centers that participate in the NAGKC.

Methods

Patient Selection

Four academic medical centers that received individual internal review board approval for retrospective clinical outcome studies participated: UPMC (7 patients), Mayo Clinic (4 patients), Université de Sherbrooke (7 patients), and University of Manitoba (1 patient). The records of these 19 patients, who underwent GKS between 1996 and 2008, were assessed by each center for inclusion. All data were stripped of patient identification information and submitted using an Excel spread sheet to the NAGKC clinical coordinating center at UPMC. Data from 2 patients were censored because of absence of evaluate outcome data, leaving 17 patients eligible for data analysis (Fig. 1). Clinical outcomes were assessed at a median follow-up period of 34 months (range 3–76.5 months). Assessment was performed during outpatient visits or by phone interviews conducted by clinical staff at each institution.

Prior to GKS, all patients underwent clinical assessment, neurological examination, and imaging studies. Magnetic resonance imaging or CT studies were performed to detect neurovascular compression, demyelinating disease, or lesions of the cerebellopontine angle or sphenopalatine. All patients were intolerant or refractory to comprehensive medical therapy (including agents such as sumatriptan, DHE-45, octreotide, verapamil, corticosteroids, and antiepileptic medications).

Study Population

This series included 3 women (18%) and 14 men (82%; Table 1). The median age of the patients was 47 years (range 26–83 years). The median duration of pain before GKS was 10 years (range 1.3–40 years). Seven patients had previously undergone unsuccessful surgical procedures. Two of these 7 patients underwent MVD, 2 underwent MVD and glycerol rhizotomy, 1 underwent unsuccessful hypothalamic DBS, and 1 underwent unsuccessful trigeminal ganglion stimulation. One patient underwent GKS (80 Gy, 4-mm collimator, delivered to the left TN) at another institution. One patient experienced mild facial weakness (House-Brackmann Grade II) and 1 patient had persistent Horner syndrome. No patient experienced trigeminal sensory loss before GKS. Fourteen patients (82%) had typical autonomic features at the time of pain attacks, including ipsilateral lacrimation (12 patients), conjunctival injection (5 patients), rhinorrea (8 patients), Horner syndrome (3 patients), hypersalivation (1 patient), and facial flushing (1 patient).

Radiosurgical Procedures

Models U, B, C, 4C, and Perfexion Gamma Knife units were used interchangeably for GKS depending on the technology available at participating centers. After application of the Leksell Model G stereotactic frame (Elekta Instruments) under local anesthesia, usually supplemented by mild intravenous sedation, patients underwent stereotactic MR imaging to identify the radiosurgical target. The MR imaging studies were performed using contrast-enhanced, short repetition time sequences and axial volume acquisitions of 512 × 216 matrices divided into 1-mm slices. When the TN was difficult to identify on images (usually because of previous surgery), additional axial MR images with long relaxation time were obtained. A single 4-mm isocenter was used for targeting the midportion of the TN root. The isocenter was usually located so that the brainstem surface was irradiated at < 30% isodose line. In 1 patient 2 isocenters were used to irradiate a longer nerve segment. Eight patients underwent SPG GKS at the same procedure. The SPG was identified by imaging the vidian canal and placing a single 8-mm isocenter 2–3-mm anterior to the end of the canal using both merged CT and MR imaging (Fig. 2). Targeting was assisted by radiologists experienced in cranial base imaging. Eight patients underwent only TN root GKS. Patients typically underwent only GKS of the TN root (before 2004 at UPMC, before 2005 at Université de Sherbrooke, before 2006 at Mayo Clinic, and no patients at the University of Manitoba), and patients typically underwent GKS for both targets of SPG and TN root (at UPMC since 2004, at Université de Sherbrooke since 2005, no patients at Mayo Clinic, and since 2004 at the University of Manitoba). The median maximum dose for the TN root was 80 Gy (range 60–97.8 Gy). One patient underwent SPG GKS alone (maximum dose of 90 Gy using 2 isocenters). The maximum dose delivered to the TN was 80 Gy in 8 patients using a single 4-mm isocenter. The dose to the SPG was 80 Gy in 6 patients and 90 Gy in 2 patients using a single 8-mm isocenter. A team consisting of a neurosurgeon, radiation oncologist, and medical physicist performed dose selection and planning. The median target volumes were 0.09 ml (range 0.087–0.190 ml) for the TN and 0.594 ml (range 0.570–0.715 ml) for the SPG.

Evaluation Criteria

All serial follow-up information was obtained from the patients or their referring physicians and included the degree of pain relief, latency interval to pain relief, need for further surgical procedures, use of medication, and new symptoms. In addition, up-to-date clinical information was obtained for all patients by telephone interviews conducted by physicians who were not involved in treatment. Clinical
results were classified according to the BNI score: Grade I (pain free, no use of medication), Grade II (occasional pain but off medication), Grade IIIa (no pain and continued use of medication required), Grade IIIb (some pain, controlled with medication), Grade IV (pain improved but not adequately controlled on medication), and Grade V (no pain relief whatsoever).27 We defined BNI Grades I–IIIb as representing favorable pain relief, whereas BNI Grades IV and V were defined as treatment failures. Recurrence was defined as a return to a preradiosurgical clinical state. The time to response after radiosurgery was analyzed using the product-limit method of Kaplan and Meier. The relationship between pain outcomes and improvement of autonomic features or development of trigeminal dysfunction were analyzed using the Fisher exact test.

**Results**

**Initial Pain Relief**

Twelve patients (71%) had favorable pain relief (BNI Grades I–IIIb) at a median of 2.9 months after GKS (range 0.5–12.2 months; Table 2; Fig. 3). Three patients (18%) had BNI Grade I, 5 (29%) had Grade IIIa, and 4 (24%) had Grade IIIb outcomes after GKS. Five patients (29%) had no or poor pain relief, including 1 patient who was Grade IV and 4 who were Grade V. One of the patients who had no or poor pain relief underwent DBS 20 months after GKS and achieved favorable pain relief (Grade IIIb) 14 months after DBS. Two patients remained at Grade IV and 3 at Grade V at the time of final follow-up.

Five (63%) of 8 patients who underwent SRS for the
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TABLE 1: Patient characteristics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Side</th>
<th>Duration of Pain Before GKS (yrs)</th>
<th>Pain Type</th>
<th>Autonomic Features</th>
<th>Prior Surgical Procedures</th>
<th>Results of Prior Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69, M</td>
<td>lt</td>
<td>10</td>
<td>episodic</td>
<td>no</td>
<td>none</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>51, M</td>
<td>rt</td>
<td>1.3</td>
<td>episodic</td>
<td>yes</td>
<td>MVD (2x) &amp; glycerol rhizotomy (1x)</td>
<td>no benefit</td>
</tr>
<tr>
<td>3</td>
<td>53, F</td>
<td>lt</td>
<td>40</td>
<td>episodic</td>
<td>yes</td>
<td>DHE-45 injection</td>
<td>no benefit</td>
</tr>
<tr>
<td>4</td>
<td>34, F</td>
<td>lt</td>
<td>18</td>
<td>episodic</td>
<td>yes</td>
<td>occipital nerve blocks &amp; DHE-45 injections</td>
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<td>5</td>
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<td>lt</td>
<td>7</td>
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<td>MVD (2x) &amp; glycerol rhizotomy (1x)</td>
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<tr>
<td>6</td>
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<td>no</td>
<td>TN stimulation</td>
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<tr>
<td>7</td>
<td>47, M</td>
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<td>NA</td>
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<td>10</td>
<td>chronic</td>
<td>yes</td>
<td>MVD</td>
<td>better, 1 year after MVD</td>
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<tr>
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<td>53, M</td>
<td>lt</td>
<td>2</td>
<td>episodic</td>
<td>yes</td>
<td>DBS</td>
<td>improved</td>
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<tr>
<td>10</td>
<td>74, M</td>
<td>lt</td>
<td>3</td>
<td>chronic</td>
<td>yes</td>
<td>supra- &amp; infraorbital nerve block</td>
<td>pain reduction for a few wks</td>
</tr>
<tr>
<td>11</td>
<td>68, M</td>
<td>lt</td>
<td>17</td>
<td>episodic</td>
<td>no</td>
<td>GKS (80 Gy, 4-mm isocenter) to left TN</td>
<td>complete pain relief for 13 mos, then recurrence</td>
</tr>
<tr>
<td>12</td>
<td>83, M</td>
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<td>13</td>
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<tr>
<td>14</td>
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<tr>
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<tr>
<td>16</td>
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<td>NA</td>
</tr>
<tr>
<td>17</td>
<td>41, M</td>
<td>rt</td>
<td>14</td>
<td>chronic</td>
<td>yes</td>
<td>MVD</td>
<td>20% pain reduction</td>
</tr>
</tbody>
</table>

* NA = not applicable.

TN root and SPG had favorable initial pain relief (Grades I–IIIb). Seven (78%) of 9 patients who underwent GKS for TN root alone (8 patients) or SPG alone (1 patient) had favorable initial pain relief.

Two of 4 patients with chronic CH had no pain relief after GKS; 1 experienced significant pain relief (BNI Grade IIIa), and 1 patient experienced complete pain relief (BNI Grade I).

Maintenance of Pain Relief

Favorable pain relief (BNI Grades I–IIIb) was maintained in 10 patients (59%; Grade I, 1 patient; Grade IIIa, 4 patients; and Grade IIIb, 5 patients) at the time of final follow-up before additional surgical procedures (Table 3). Three patients (18%) had additional surgical procedures (DBS, 1 patient; repeat GKS, 2 patients), and the remaining 10 patients (59%) attained pain relief classified as Grade I (1 patient), Grade IIIa (4 patients), or Grade IIIb (5 patients) at the time of final follow-up. Two patients experienced pain recurrence after initial favorable pain relief 7 and 46 months after GKS; both patients had undergone TN root and SPG GKS. One of these patients had pain recurrence with autonomic features after initial favorable pain relief (Grade IIIa) and underwent repeat GKS 51 months after the initial procedure. At the time of repeat GKS, both the TN (maximum dose 60 Gy, single 4-mm isocenter) and the SPG (maximum dose 70 Gy, single 8-mm isocenter) were irradiated. The patient experienced complete pain relief (Grade I) without subsequent pain relapse or autonomic feature 3.5 months after repeat GKS. The other patient experienced no additional surgical treatment at the time of the last follow-up evaluation. The rate of maintenance of pain relief (Grades I–IIIb, excellent to favorable pain relief) after GKS was 91, 91, and 73% at 1, 2, and 4 years, respectively (Fig. 4).

Two patients with chronic CH who attained significant pain relief (Grade I, 1 patient; Grade IIIa, 1 patient) after SRS had no pain recurrence. In this small experience we could not determine a relationship between chronic CH
and the likelihood of pain recurrence (p = 0.555, log-rank test).

Outcome of Autonomic Features

Two patients who did not have autonomic features showed pain improvement (Grades I and IIIa) after GKS. One patient who did not have autonomic features experienced treatment failure (Grade V). Seven (50%) of 14 patients who had autonomic features showed improvement in their autonomic features after GKS. One patient had improvement in his autonomic features but poor pain relief (Grade IV). Three (43%) of 7 patients who had favorable pain relief (Grades I–IIIb) and 4 patients (57%) who showed treatment failure (Grades IV–V) after GKS nonetheless had reduced autonomic features after GKS. In the Fisher exact test, pain relief (Grades I–IIIb) was not associated with improvement of autonomic features (p = 0.107).

Sensory Findings After Radiosurgery

Four (50%) of 8 patients who had both the TN and the SPG irradiated developed trigeminal dysfunction. Four (50%) of 8 patients who underwent GKS only to the TN also developed trigeminal dysfunction. Three patients developed trigeminal sensory loss (hypesthesia), 2 developed paresthesias but no sensory loss, and 1 developed paresthesias and sensory loss after GKS. One patient developed profound sensory loss and deafferentation pain (80 Gy TN dose) after GKS. No other side effect or other complications occurred after radiosurgery. Five (50%) of 10 patients who had favorable pain relief (Grades I–IIIb) after GKS developed trigeminal dysfunction after GKS. Three (43%) of 7 patients who did not improve after GKS also developed trigeminal dysfunction. Using the Fisher exact test, pain relief (Grades I–IIIb) was not associated with the development of trigeminal dysfunction (p = 0.778).

Discussion

Cluster headache includes both episodic and chronic cluster variants. Episodic CHs are by far most common, accounting for 80–90% of patients with CH.1,20 This
type of CH is characterized by several attacks of periorbital pain each day during 6–12-week periods, followed by pain-free intervals that typically last 6–12 months. Chronic CH is characterized by the absence of sustained periods of remission. Our series included 13 patients with episodic CH and 4 with chronic CH. In this study the type of CH was not associated with the probability of pain relief after GKS.

Cluster headaches may be associated with ipsilateral autonomic symptoms that include Horner syndrome, rhinorrhea, conjunctival injection, lacrimation, and facial flushing. Horner syndrome appears to be secondary to an ipsilateral sympathetic dysfunction of postganglionic fibers. Hyperactivity of cranial parasympathetic fibers from the cranial nerve VII also potentiate autonomic symptoms such as lacrimation. In our series, 14 patients had autonomic symptoms, but the presence of autonomic symptoms did not correlate with either initial or persistent pain relief.

Because the pain of a CH peaks quickly and only lasts briefly, over-the-counter pain medications usually are not effective. Other rapid onset agents may provide pain relief and include sumatriptan, dihydroergotamine, and octreotide. Oxygen inhalation can provide rapid pain relief, but such therapy is cumbersome and impractical for most patients. Episodic CH may be very difficult to manage in some patients, especially those with medical comorbidities such as cardiovascular disease and diabetes mellitus; as such, patients may poorly tolerate therapies. Because approximately 20% of patients with chronic CH are highly refractory to medical treatment, various surgical alternatives have been attempted. These alternatives include alcohol injection in the gasserian ganglion, root sectioning of the TN, glycerol rhizotomy, radiofrequency rhizolysis of the TN, MVD of the TN and/or the nervus intermedius, and DBS of the posterior hypothalamus. All such surgical interventions are associated with varying degrees of success and potential morbidity. Cluster headache may also be known as histamine headache, Horton headache, paroxysmal nocturnal cephalgia, and sphenopalatine neuralgia. Sanders and Zuurmond reported a series of 66 patients with CH, all of who were treated with radiofre-
frequency lesioning of the SPG. In their series, 56% had complete pain relief and 26% had partial pain relief without long-term side effects. Pieper et al. reported on a series of 18 patients with CH who were treated with percutaneous retrogasserian glycerol rhizotomy. Fifteen patients (83%) obtained immediate pain relief after 1 or 2 injections. Cluster headache recurred in 7 patients (39%) over the course of the study. Fourteen patients reported some sequelae after percutaneous retrogasserian glycerol rhizotomy, which included facial hypesthesia (but not anesthesia) in 11 patients and mild corneal hypesthesia in 7 patients. Although both radiofrequency lesioning and glycerol rhizotomy are more likely to lead to detectable sensory dysfunction than GKS, the differences in response between these various surgical procedures cannot be determined at present. Gamma Knife surgery in patients with trigeminal neuralgia leads to pain relief in most, even though less than 10% of patients develop sensory loss. This clinical finding is at odds with the histopathological observations in primates who undergo trigeminal GKS, in which destructive effects are observed in both unmyelinated and heavily myelinated fibers. Recently GKS has been used to treat CH. Ford et al. reported 6 patients with refractory CH, 4 of whom achieved excellent pain relief, 1 good pain relief, and 1 fair pain relief days to weeks after GKS. No patient experienced significant side effects when studied 8–14 months afterward. These investigators selected a GKS dose of 70 Gy delivered to the TN. Donnet et al. reported on 10 patients with drug-resistant CH: 2 patients had complete pain relief, 1 had a good result (although the pain evolved to the episodic form), but 7 experienced no improvement after an average follow-up of 3 years. The TN target dose was 80–85 Gy in this study. Nine patients developed a new trigeminal neuropathy, including 3 patients with paresthesias and 6 with sensory loss. McClelland et al. reported on 10 patients with refractory CH. One patient in this study obtained fair pain relief and 9 had poor pain relief after an average follow-up of 40 months. Six patients had initial benefit but late pain relapse. Five patients developed trigeminal sensory loss. The TN in this series received a maximum dose of 75 Gy.

More recently, based on new hypotheses related to the pathophysiology of CH, the SPG has been added as a potential therapeutic target. Pollock and Kondziolkta reported on a patient with sphenopalatine neuralgia who experienced initial pain relief after SPG GKS but required repeat GKS 17 months later. Two years following SRS, the patient was pain free and had no residual vasomotor symptoms. Although distinguished from CH, SPG neuralgia is characterized by some overlapping clinical symptoms.

At a recent meeting of the Leksell Gamma Knife Society, De Lothiniere et al. (De Lothiniere ACJ, Knisely JP, Bond JE, presented at the 12th International Meeting of the Leksell Gamma Knife Society, 2004) reported on 7 patients with CH who had both the TN and the SPG irradiated. These authors used a 4-mm collimator to target the TN (80–90 Gy maximal dose) and an 8-mm collimator to target the SPG (90 Gy maximal dose). At 3 years follow-up, 5 patients had excellent pain relief, 1 had greater than 50% pain reduction, and 1 patient (with bilateral CH) experienced excellent relief on 1 side and poor relief on the other. Four of 7 patients developed sensory loss in the V2 distribution. Two patients required repeat GKS due to pain recurrence, but eventually obtained good pain relief after repeat GKS.

In our series, both the TN root and the SPG were targeted in 8 of 17 patients. Twelve patients (71%) experienced initial pain relief. However, 2 who had initial pain relief developed pain recurrence at the intervals of 7 and 46 months. One patient underwent repeat GKS and achieved an outcome of Grade I at final follow-up. One patient with an initially poor response to GKS underwent DBS and achieved a good outcome (Grade IIIb) at final follow-up. Ultimately, 10 patients (59%), none of whom underwent additional surgery, experienced favorable pain relief after GKS.

In this series, one-half of the patients undergoing TN GKS developed TN dysfunction. The detection of post-GKS trigeminal sensory dysfunction was the same in patients who had only the TN targeted as it was in patients who had both the TN and SPG targeted. In our current series of GKS for patients with trigeminal neuralgia, only 10% developed trigeminal dysfunction by 2 years. In other large series, trigeminal dysfunction after GKS varied from 10 to 37%. Donnet et al. proposed reasons why patients with CH may have a higher rate of trigeminal dysfunction, including a possible increased TN sensitivity to radiation in patients with CH as compared with patients with trigeminal neuralgia. The reason for this variance is unknown.

In his proposed classification of facial pain, Burchiel described trigeminal neuralgia Types 1 and 2, trigeminal neuropathic pain, trigeminal deafferentation pain, symptomatic trigeminal neuralgia (from multiple sclerosis), postherpetic neuralgia, and atypical pain related to a somatoform pain disorder. He argued that constant versus episodic pain may stem from hyperactivity of small myelinated or unmyelinated axons rather than large myelinated fibers. Although the neurophysiology of CH remains unknown, our study suggests that patients with this disorder are more sensitive to axonal degeneration and sensory dysfunction after radiosurgery.

Conclusions

Gamma Knife surgery for medically intractable refractory CH is a minimally invasive alternative surgical treatment that provides early pain relief in the majority of patients, but is associated with a higher risk of trigeminal sensory loss than occurs after GKS for patients with typical trigeminal neuralgia. At 3 years, approximately 60% of the patients in this series had persistent pain improvement without the need for additional surgical procedures. This preliminary report cannot clearly define any benefit to adding SPG radiosurgery to the usual TN target. In the future, a prospective trial that compares a single target of the TN root (TN GKS) to dual targets of both the TN and SPG (TN and SPG GKS) may provide further understanding of the value of GKS for cluster headaches. Such a proposed trial is currently under evaluation by the NAGKC.
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Disclosure

Drs. Lunsford, Kondziolka, and Niranjan are consultants with AB Elekta. Dr. Lunsford is a stockholder in AB Elekta. The work described in this report was funded by a grant to Dr. Kano from the Osaka Medical Research Foundation for Incurable Diseases and the Japan Brain Foundation.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lunsford, Kano, Kondziolka, Mathieu, Pollock. Acquisition of data: Kano, Mathieu, Flannery, Pollock, Kaufmann. Analysis and interpretation of data: Kano. Drafting the article: Lunsford, Kano, Mathieu, Pollock, Kaufmann. Critically revising the article: Lunsford, Kano, Kondziolka, Mathieu, Starr, Niranjan, Pollock, Kaufmann, Flickinger. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Kano. Study supervision: Lunsford, Kondziolka, Pollock.

Acknowledgments

For this report of the NAGKC, outcome data were provided by the UPMC, the Mayo Clinic, the Université de Sherbrooke, and the University of Manitoba.

References