Gamma Knife Radiosurgery for Trigeminal Neuralgia

Results and Expectations

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Background: Trigeminal neuralgia is a disabling pain syndrome responsive to both medical and surgical therapies. Stereotactic radiosurgery using the gamma knife can be used to inactivate a specified volume in the brain by cross firing 201 photon beams. We evaluated pain relief and treatment morbidity after trigeminal neuralgia radiosurgery.

Methods: All evaluable patients (n = 106) had medically or surgically refractory trigeminal neuralgia. A single 4-mm isocenter of radiation was focused on the proximal trigeminal nerve just anterior to the pons. For follow-up an independent physician who was unaware of treatment parameters contacted all patients.

Results: After radiosurgery, 64 patients (60%) became free of pain and required no medical therapy (excellent result), 18 (17%) had a 50% to 90% reduction (good result) in pain severity or frequency (some still used medications), and 9 (9%) had slight improvement. At last follow-up (median, 18 months; range, 6-48 months), 77% of patients maintained significant relief (good plus excellent results). Only 6 (10%) of 64 patients who initially attained complete relief had some recurrent pain. Radiosurgery dose (70-90 Gy), age, surgical history, or facial sensory loss did not correlate with pain relief. Poorer results were found in patients with multiple sclerosis. Twelve patients developed new or increased facial paresthesias after radiosurgery (10%). No patient developed anesthesia dolorosa. There was no other procedural morbidity.

Conclusions: Gamma knife radiosurgery is a minimally invasive technique to treat trigeminal neuralgia. It is associated with a low risk of facial paresthesias, an approximate 80% rate of significant pain relief, and a low recurrence rate in patients who initially attain complete relief. Longer-term evaluations are warranted.

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Medical management remains the mainstay of treatment for trigeminal neuralgia. Several effective surgical techniques exist and are used when medical therapy is ineffective or associated with significant adverse effects. Despite high rates of initial success for virtually all surgical procedures, most physicians and patients choose medical therapy first because of potential surgical morbidity, the risk for loss of facial sensation after surgery, or recurrent pain despite initial surgical success. The use of an external energy source as a surgical tool to manage trigeminal neuralgia has a long history. Various techniques include radiofrequency, generated thermal energy (percutaneous rhizotomy), mechanical energy (balloon compression), and physical energy (surgical nerve section). Microvascular decompression aimed at removing the cause of trigeminal neuralgia or chemical manipulation of the nerve, such as that performed in glycerol rhizotomy, are other techniques with proven efficacy. Despite these options, significant problems continue to permeate the management of this pain. Despite medical or surgical therapy, these problems range from persistent or recurrent typical trigeminal neuralgia to the tendency for pain to occur in elderly patients. Elderly patients are prone to have concurrent medical illnesses that warrant a minimally invasive approach. In addition, a spectrum of pain disorders exists, with some patients having typical neuralgic pain and others reporting constant or atypical facial pain.

Initially, we sought to reevaluate the early anecdotal success of trigeminal neuralgia radiosurgery reported by Leksell. During the 1970s and 1980s, several surgeons irradiated the trigeminal gan-
SUBJECTS, MATERIALS, AND METHODS

One hundred twenty-one consecutive patients underwent gamma knife radiosurgery for typical trigeminal neuralgia. The mean patient age was 67 years (age range, 32-92 years) and the mean duration of pain was 11 months. All patients underwent comprehensive trials of medical therapy that included carbamazepine. Many patients also received phenytoin sodium, baclofen, and/or gabapentin, alone or in combination with carbamazepine. Prior surgeries included microvascular decompression (n = 42), glycerol rhizotomy (n = 57), or radiofrequency rhizotomy (n = 19). No patient had anesthesia dolorosa. The right side of the face was affected in 72 patients (59.5%) and the left side in 49 (40.5%). Pain involved the V1, V2, or V3 distributions, alone or in combination. The most common distribution was combined V2 and V3 pain. Forty-six patients described some degree of facial numbness (Table). Indications for radiosurgery included failure of pharmacologic treatment to provide significant pain relief, failure of prior surgery, or significant adverse effects from medication. Failure of previous therapy was defined as persistent disabling pain lasting a minimum of 1 month since initiation of the prior therapy. Radiosurgery was performed with informed consent and different surgical alternatives were explained to the patients. All patients in this series had idiopathic trigeminal neuralgia or trigeminal neuralgia secondary to multiple sclerosis. We excluded from this analysis patients with trigeminal neuralgia related to tumors. All patients underwent brain imaging scans (computed tomographic or MRI) to exclude the presence of a mass lesion prior to radiosurgery. Vascular compression of the trigeminal nerve was not a contraindication to radiosurgery.

RADIOSURGERY TECHNIQUE

All patients underwent stereotactic radiosurgery using a gamma knife (Leksell Gamma Knife, Elekta Instruments, Atlanta, Ga). One gamma knife (model U) was used to operate on 79 patients and another gamma knife (model B) in 42 patients. The dose profile of the 4-mm isocenter is multiple planes. Volume acquisition sequences using 512 × 256 matrices were divided into 1-mm image slices to provide graphic depiction of the trigeminal nerve. After application of the stereotactic frame (Leksell model G stereotactic frame, Elekta Instruments), all patients underwent stereotactic MRI to identify the trigeminal nerve. Magnetic resonance imaging sequences were performed using short repetition time sequences and contrast enhancement in multiple planes. Volume acquisition sequences using 312 × 256 matrices were divided into 1-mm image slices to provide graphic depiction of the trigeminal nerve and pons (Figure 1). The nerve was identified as it followed its course from the pons into the Meckel cave. In some patients who had undergone prior surgery (microvascular decompression or percutaneous surgery), the nerve was difficult to identify (either because of nerve atrophy or regional perineural fibrosis) and thus long repetition time MRI sequences were used to identify the nerve against the high-signal background of cerebrospinal fluid. Stereotactic coordinates were calculated for a single 4-mm isocenter placed 2 to 4 mm anterior to the junction of the trigeminal nerve and pons (Figure 1). The isocenter was positioned so that the brainstem surface was usually irradiated at no more than the 30% isodose. Dose planning was performed using a high-speed work station and computer image integration. Radiosurgery planning and dose selection were performed by the neurologic surgeon, radiation oncologist, and medical physicist. The range of maximum radiosurgery dose was between 70 and 90 Gy; 70 Gy commonly was used for patients who had not undergone prior surgery and 80 to 90 Gy was prescribed for patients with recurrent pain after prior surgery, although a strict protocol did not exist. We acknowledged the potential for selection bias for a higher dose in patients believed to have more refractory pain.

All patients were discharged within 24 hours after radiosurgery. Patients were studied according to the degree of pain relief, latency interval to pain relief, onset of paresthesia, need for further surgical treatment, and complications. Patient evaluations were made by a physician who did not participate in the procedure and who was blinded to radiation dose. Since all patients had lancinating pain, pain relief was determined by the outcome of this pain type both in terms of its severity and frequency.

STATISTICAL ANALYSIS

Univariate comparisons of response rates were made using the Pearson x² test or 2-tailed Fisher exact test, depending on the number of patients in the matrix. Multivariate analysis of response rates was performed with stepwise logistic regression. The percentage of patients with pain control was calculated as a product of the response rates and freedom from relapse rate.10,11 Significance was defined as P < .05.
RESULTS

PAIN RELIEF

Median follow-up after radiosurgery was 18 months (range, 6-48 months). Relief from pain was coded by the patients into 4 categories. These included no response, slight improvement (10%-50% improved), good response (50%-90% improved but still using medications if used preoperatively), and excellent response (100% free of pain and not taking medication). No response or slight improvement was referred to as a treatment failure. Criteria for improvement included a reduction in both the frequency and severity of trigeminal neuralgia (lancinating pain) attacks. Patients with good results continued to take medication (although usually reduced) if they had done so before radiosurgery. These patients described either a significant decrease in the frequency of attacks and/or decreased intensity of individual attacks. Median time to response was 4 weeks (range, 1 day to 3 months).

One hundred six (87%) of 121 patients were examined and complete follow-up data about pain relief and morbidity are summarized as follows:

<table>
<thead>
<tr>
<th>Pain Result*</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent (no pain)</td>
<td>64 (60)</td>
</tr>
<tr>
<td>Good (50%-90% decrease)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Poor (&lt;50% relief)</td>
<td>24 (23)</td>
</tr>
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</table>

*Patient’s description of change in the frequency or severity of lancinating pain.

Initial improvement in trigeminal neuralgia was noted in 91 patients (86%). At last follow-up, significant pain relief was noted by 77% of patients (good plus excellent results). Relapse in pain was noted in only 6 (10%) of 64 patients who attained complete relief from 2 to 10 months after onset of complete relief.

PAIN RESPONSE AND RADIOSURGERY DOSE

A maximum dose of 70 Gy was delivered to 54 patients. The median duration of trigeminal neuralgia was 12 months and median follow-up after radiosurgery, 19 months. Five patients had multiple sclerosis.

Sixty patients received a maximum dose of 80 Gy. The median duration of prior pain was 10 months, and median follow-up after radiosurgery, 16 months. Five of these patients had multiple sclerosis.

Five patients received a maximum dose of 85 Gy. Two patients received a maximum dose of 90 Gy. One of these patients had multiple sclerosis and the other multiple prior surgeries. There was no significant difference in pain relief when we compared 70 Gy (10-80 Gy) ($P = .57$) for complete pain relief and $P = .37$ for good plus excellent results).

OTHER CRITERIA

We compared specific factors with degree of pain relief. For onset of complete pain relief, age proved insignificant ($P = .75$) as did sex ($P = .22$) or history of prior sur-
Radiosurgery is the least invasive surgical procedure for trigeminal neuralgia. In the present series, and in both our multi-institution study and the report by Young et al, no systemic morbidity was found. No patient sustained any form of neurologic morbidity other than a low risk for facial numbness. In the multi-institution study, 3 (6%) of 50 patients developed increased facial paresthesia after radiosurgery. Young et al noted that only 1 of 60 patients had increased facial sensory loss. This occurred in a patient with a trigeminal schwannoma. In our study we found a 10% rate of partial facial numbness. We initially believed this slightly higher rate was because of some higher radiosurgery doses (80-90 Gy), and selection of patients who already had some numbness. However, these factors did not prove to be significant. All patients were contacted for an evaluation of pain relief and adverse effects every 6 to 12 months. Although use of a randomized treatment schema that incorporates preoperative and postoperative pain rating scales would have been a more powerful tool to evaluate the response to radiosurgery, we used an independent physician blinded to the radiation parameters for data collection from patients. All data were from the patients' own descriptions of their clinical status. The absence of infection, cerebrospinal fluid leakage, anesthesia complications, hearing loss, facial hematoma, facial weakness, or brainstem injury has established radiosurgery as an attractive surgical alternative for many patients.

Despite these advantages, the use and evaluation of radiosurgery has proceeded slowly. Leksell first used radiosurgery techniques for trigeminal nerve irradiation in 1953. Results from these 2 patients (both were free of pain after delays of 1-5 months) were not published until 1971. Leksell concluded that “from these observations no definite conclusion should be drawn concerning the optimal dose of radiation or the exact mechanism in site of action in the route or ganglion, or even the general applicability of the method.” In 1983, Leksell noted that 63 patients had undergone gamma knife radiosurgery for trigeminal neuralgia. He did not describe the surgical method or results. Lindquist et al (n = 46) and Rand et al (n = 12) reported on the use of gasserian ganglion radiosurgery but inconsistent results were obtained. These authors concluded that the ganglion was probably not appropriate as the primary radiosurgery target.

DEVELOPMENT OF THE TECHNIQUE

During the last 5 years, we and others have worked to determine the kind of patient who would benefit from trigeminal neuralgia radiosurgery, determine the appropriate radiation dose, and clarify expectations. It was not known how much radiation was necessary to relieve pain quickly, maintain that relief over the long-term, and do so with no systemic morbidity and minimal chance for facial sensory loss. To answer this question, we formed a multicenter study group and compared data from patients who had undergone radiosurgery at doses from 60 to 90 Gy. All groups selected the proximal nerve and root entry zone as the radiation target that could be identi-
fied on MRI scans and targeted with the gamma knife. Because the nerve was myelinated by oligodendrocytes and perhaps was more sensitive to irradiation than myelin from Schwann cells, we hypothesized that a stronger radiobiological effect would occur at this portion of the nerve.15,25,26 We also believed that the compact union of fibers from different nerve divisions would facilitate irradiation of a smaller volume target. We attributed the observation of good or excellent results to high-resolution identification of the trigeminal nerve near the pons and accurate radiosurgical targeting.27 In that study, a maximum dose of at least 70 Gy was identified for a higher rate of pain relief. Radiosurgical targeting was found to be accurate as previously identified in rat and primate brain models and in the clinical use of radiosurgery for the management of other disorders, such as acoustic tumors, pituitary microadenomas, and brain metastases, using the same 4-m gamma knife collimator.22 From these findings, we examined a large series of patients using standard techniques and a narrow radiosurgery dose range (70-90 Gy).

Current studies at our center include a randomized trial that compares 1 with 2 radiosurgery isocenters (with 2 isocenters, a greater length of nerve is irradiated) to determine the effect of nerve length on pain relief. We have also begun a study of the histological and ultrastructural effects of trigeminal nerve radiosurgery in a large animal model.

MECHANISMS OF PAIN RELIEF AFTER RADIOSURGERY

It is unclear why trigeminal nerve irradiation causes relief of trigeminal neuralgia pain. We speculate that nerve irradiation leads to functional electrophysiologic block of ephaptic transmission since most patients maintain normal trigeminal function.28 Although we do not perform follow-up imaging routinely, MRI studies performed 6 to 24 months after radiosurgery show contrast enhancement at the target (Figure 2). Radiosurgery performed on patients with cavernous sinus tumors has been associated with low rates of trigeminal dysfunction.29 Radiosurgery may have an effect on ephaptic transmission but not on normal axonal conduction. Young et al23 theorized that radiofrequency energy may interrupt both abnormal transmission and normal axonal conduction in such a way that loss of normal facial sensation is required for long-lasting pain relief. Perhaps radiation energy has a larger therapeutic ratio between pain relief and sensory loss. Our group recently reported pain relief from sphenopalatine neuralgia after radiosurgery. In this procedure the sphenopalatine ganglion was irradiated with an 8-mm collimator to a maximum dose of 90 Gy.30

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REFERENCES