Stereotactic radiosurgery for trigeminal neuralgia: a multiinstitutional study using the gamma unit

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A multiinstitutional study was conducted to evaluate the technique, dose-selection parameters, and results of gamma knife stereotactic radiosurgery in the management of trigeminal neuralgia. Fifty patients at five centers underwent radiosurgery performed with a single 4-mm isocenter targeted at the nerve root entry zone. Thirty-two patients had undergone prior surgery, and the mean number of procedures that had been performed was 2.8 (range 1–7). The target dose of the radiosurgery used in the current study varied from 60 to 90 Gy. The median follow-up period after radiosurgery was 18 months (range 11–36 months). Twenty-nine patients (58%) responded with excellent control (pain free), 18 (36%) obtained good control (50%–90% relief), and three (6%) experienced treatment failure. The median time to pain relief was 1 month (range 1 day–6.7 months). Responses remained consistent for up to 3 years postradiosurgery in all cases except three (6%) in which the patients had pain recurrence at 5, 7, and 10 months. At 2 years, 54% of patients were pain free and 88% had 50% to 100% relief.

A maximum radiosurgical dose of 70 Gy or greater was associated with a significantly greater chance of complete pain relief (72% vs. 9%, p = 0.0003). Three patients (6%) developed increased facial paresthesia after radiosurgery, which resolved totally in one case and improved in another. No patient developed other deficits or deafferentation pain. The proximal trigeminal nerve and root entry zone, which is well defined on magnetic resonance imaging, is an appropriate anatomical target for radiosurgery. Radiosurgery using the gamma unit is an additional effective surgical approach for the management of medically or surgically refractory trigeminal neuralgia. A longer-term follow-up review is warranted.

KEY WORDS • trigeminal neuralgia • tic douloureux • stereotactic radiosurgery • facial pain

Lars Leksell’s first radiosurgical procedure in 1951 was undertaken for the treatment of trigeminal neuralgia. In that first case, he aimed the radiation beam generated by an orthovoltage x-ray tube at the trigeminal ganglion using a conventional stereotactic frame system. The use of an external energy source as a surgical tool to manage trigeminal neuralgia has a long history, including radiofrequency-generated thermal energy for percutaneous rhizotomy and mechanical energy for balloon compression. Other techniques with proven substantiated efficacy include microvascular decompression, percutaneous retrogasserian glycerol rhizotomy, and nerve section. This surgical armamentarium has been used in patients with typical trigeminal neuralgia that has proved refractory to, or intolerant of, comprehensive medical management. Despite the initial success of many surgical procedures, some patients have exhibited persistent or recurrent typical trigeminal neuralgia. Such patients are often elderly, many of whom have concurrent medical illnesses that warrant use of a minimally invasive therapeutic approach.

We sought to reevaluate the early anecdotal success of trigeminal neuralgia radiosurgery reported by Leksell. Subsequent pilot studies on irradiation of the trigeminal root entry zone and proximal nerve were performed by Håkanson and Lindquist at the Karolinska Institut. Our hypothesis was that with the aid of stereotactic high-resolution magnetic resonance (MR) imaging to define the trigeminal nerve, we could relieve pain and preserve facial sensation using radiosurgery. We suspected that radiosurgery would be a useful adjuvant or an alternative surgical strategy in patients who have trigeminal neuralgia. The goals of our study were: 1) to identify both short- and long-term outcomes of radiosurgery for trigeminal neural-
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Clinical Material and Methods

Patient Population

Patients were accepted for stereotactic radiosurgery at five different health care institutions. A total of 50 patients with typical trigeminal neuralgia underwent radiosurgery using similar technology and method of trigeminal nerve targeting. No patient experienced constant pain, burning pain, dysesthesia, or anesthesia dolorosa. The numbers of patients at each institution were as follows: 14 patients in Pittsburgh, PA, 14 in Seattle, WA, 12 in Los Angeles, CA, eight in Marseille, France, and two patients in Providence, RI. The mean patient age was 70 years (range 40–87). Twenty patients were men and 30 were women.

In the group of 32 patients who had undergone prior surgery, the mean number of prior procedures performed per patient was 2.8 (range 1–7). Eighteen patients (36%) had not had prior surgery before radiosurgery. The number of patients undergoing specific numbers of prior operations and the types of procedures is detailed in Table 1.

Radiosurgical Technique

All patients underwent stereotactic radiosurgery using the Leksell Gamma Unit (Elekta Instruments, Atlanta, GA). At facilities in the United States, the Model U Gamma Unit was used; in Marseille the Model B unit was used. The dose profile of the 4-mm isocenter is similar between the two units. Radiosurgery was performed after local anesthesia was induced in the patient and supplemented with mild sedation.

After application of the Leksell Model G stereotactic frame (Elekta Instruments), all patients underwent ste-

![FIG. 1. Volume acquisition contrast-enhanced magnetic resonance images (short TR) obtained at 1-mm slice intervals showing the left trigeminal nerve in an 83-year-old man who underwent two prior glycerol rhizotomies. a: Axial and coronal views. b: Images showing targeting of the nerve. A single 4-mm isocenter was used to irradiate the trigeminal nerve; on the axial image the inner circle shows the 50% isodose and the outer circle, the 10% isodose. A maximum dose of 70 Gy was administered. The patient has been pain free for the past 19 months.](image-url)
A range of maximum radiosurgical doses was selected between 60 and 90 Gy. An optimum dose for safety and efficacy was not known but was believed to be within this range. Doses administered at each center included: 60, 65, 70, and 80 Gy at Pittsburgh; 60, 65, 70, and 75 Gy at Los Angeles; 70 Gy at Seattle; 70, 75, 80, and 90 Gy at Marseille; and 80 Gy at Providence. The numbers of patients treated at each dose were as follows: eight patients at 60 Gy, three at 65 Gy, 27 at 70 Gy, two at 75 Gy, six at 80 Gy, and four patients at 90 Gy. Initially, we hypothesized that the high-dose range (≥70 Gy) might be associated with faster pain relief but might also include a greater chance for postoperative facial sensory loss. Thus, as part of a dose-escalation study, some patients were treated at a lower dose range (60–65 Gy). We believed that at the lower doses, pain relief could be achieved while retaining a better chance at maintaining facial sensation. Because some centers chose a single or smaller dose range, we acknowledged the potential for selection bias (perhaps patients whose symptoms proved more refractory received a higher dose).

All patients were discharged within 24 hours after radiosurgery. Patients were studied according to their degree of pain relief, latency interval to pain relief, need for further surgical treatment, and complications.

### Statistical Analysis

Response rates and freedom from subsequent relapse were calculated using the product limit method of Kaplan and Meier.7 The percentage of patients with pain control was calculated as the product of the response rates and freedom from relapse rate.24 Univariate comparisons of response rates among different groups were performed using the Fisher’s exact test. Multivariate analysis of response rates was performed using the proportional hazards model of Cox.3

### Results

#### Pain Relief

Relief from pain was coded by the patients and their surgeons into three categories. These included poor response (0%–<50% improvement); good response (50%–90% improvement); and excellent response (100% pain free). The number of patients with “pain improvement” was calculated as the sum of the numbers in the good and excellent groups. Criteria for improvement included a reduction in both the frequency and severity of trigeminal neuralgia attacks. Patients with good results continued to take medication therapy (although usually reduced) if they had done so before radiosurgery. Most patients with excellent results after radiosurgery were able to discontinue their course of medications. The median follow-up duration after radiosurgery was 18 months (range 11–36 months). As of their last follow-up examination, of 50 patients with typical trigeminal neuralgia, 28 (56%) had excellent results, 16 (32%) had good results, and six (12%) experienced therapy failure. The median time to response was 1 month (range 1 day–6.7 months).

### Table 2

<table>
<thead>
<tr>
<th>Irradiation Dose (Gy)</th>
<th>Excellent (100% pain free)</th>
<th>Good (50%–90% relief)</th>
<th>Poor (0%–&lt;50% relief)</th>
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*Outcome as of patients’ last follow-up examination (median 18 months). — = not applicable.
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The response rates were 94% and 58% for greater than 50% pain relief and complete pain relief, respectively, at 2 years. The percentage of patients with pain relief over time is depicted in Fig. 2 upper. Three patients had recurrence of pain 5, 7, and 10 months after an initial good result (one of these had been pain free) and underwent additional surgery. Two years after radiosurgery 54% of patients were pain free and 88% had at least 50% pain relief. One patient not counted in this total had recurrence of pain after an initial excellent response and thus that therapy has been coded as a failure.

Pain Response and Radiosurgical Dose

The number of patients with pain relief differed according to the dose administered, as shown in Table 2. The response over time is shown in Fig. 2 center and lower. The proportion of patients achieving complete pain relief was significantly greater (p = 0.0003) in patients who received at least 70 Gy (28 (72%) of 39 patients) as compared to 60 to 65 Gy (one (9%) of 11 patients). The proportion of patients who maintained complete pain relief as of their last follow-up examination also was significantly greater (p = 0.0009) when a dose of 70 Gy or greater was delivered.

Prior Surgery

Thirty-two patients had undergone prior surgery for trigeminal neuralgia; 18 patients had radiosurgery as their first surgical procedure. Patients who had not undergone a prior surgical procedure tended to have better outcomes (p = 0.14) than those who had prior surgery, although this finding was not significant. Multivariate analysis of the complete response rate identified dose as the only significant variable (p = 0.016, hazards ratio 1.71/10 Gy, 95% confidence interval 1.12–2.61). We identified no differences in outcome depending on the type of prior trigeminal neuralgia surgery performed. Patient age and sex were not significant predictors of outcome in univariate or multivariate analysis (Table 3). Both patients with multiple sclerosis–related trigeminal neuralgia responded to radiosurgery with 70 Gy.

Postradiosurgical Complications

Three patients (6%) developed increased facial paresthesia and decreased sensation after radiosurgery at 65, 70, and 75 Gy. In one patient these symptoms resolved completely after 6 weeks; in another subtotal improvement occurred. No patient developed deafferentation pain after radiosurgery. There was no other neurological or systemic morbidity caused by treatment.

Discussion

In 1971, Lars Leksell discussed results from two patients who underwent radiosurgery for trigeminal neuralgia in 1953.16 Both patients had closed-skull irradiation of the trigeminal ganglion using stereotactic guidance. The first patient was treated with a total dose of 16.5 Gy and had resolution of pain after a delay of 2 weeks. This patient became pain free after 5 months and over the ensuing 18 years experienced no trigeminal neuralgia. The second patient was treated with a total dose of 22 Gy and exhibited marked improvement 1 day after radiosurgery. He experienced no trigeminal neuralgia for the next 17 years of follow-up review. Leksell stated that, “from these observations no definite conclusion should be drawn concerning the optimal dose of radiation or the exact mechanism and site of action in the root or ganglion, or even the general applicability of the method.”16 Twelve years later, Leksell provided an overview of stereotactic radiosurgery using the gamma unit; in tabular form he specified that 63 patients were treated for trigeminal neuralgia. However, no results were presented.14 Radiosurgery was also used by Leksell and colleagues to create thalamic lesions in patients suffering from intractable pain and to perform capsulotomy for patients suffering from intractable psychiatric disorders.13,17,26

In 1991, Lindquist, et al.,18 reported 46 cases of patients who had gasserian ganglion radiosurgery; 24 of these patients had skull landmarks used during conventional x-ray target localization and 22 had target localization aided by stereotactic cisternography. No dose recommendations were made. Thirteen of the 22 patients localized by cisternography were pain free after 6 months but only four remained so after 2.5 years. Rand and colleagues23 reported on 12 patients who had radiosurgery to the gasserian ganglion; seven were treated with an 8-mm collimator and five with a 4-mm collimator. Localization was performed using computerized tomography (CT) or MR imaging, and maximum doses varied from 57 to 75 Gy. Seven patients experienced complete relief or improvement in their trigeminal neuralgia, and no complications were observed. Because some patients did not respond, the authors concluded that the gasserian ganglion was probably not appropriate as the primary radiosurgery target.
would occur at this portion of the proximal nerve. Second, we believed that the compact union of fibers from different divisions would facilitate irradiation of the entire nerve with the smallest volume of energy (4-mm collimator). Third, because the nerve is a separate structure that can be identified clearly with MR imaging as it traverses the cerebrospinal fluid of the posterior fossa, we were confident in our ability to target the nerve. Because the nerve in the region of the ganglion is not identified as a separate structure, but rather implied because of its location, targeting in this area is indirect. Thus, we believe that the high numbers of patients with good or excellent results observed in this study could be attributed to excellent visualization of the trigeminal nerve near the pons and the radiobiological effect of irradiating the nerve in this location.

Because we hoped to find a dose–response relationship in trigeminal nerve irradiation, patients were treated according to a dose-stratification regimen. In Pittsburgh, consecutive patients were given radiation therapy in groups of five beginning with a dose of 60 Gy. We were able to determine a significant difference in pain control in patients who had a maximum dose of at least 70 Gy (p = 0.03 for pain control (good or excellent result) and p = 0.02 for a pain-free result). However, higher doses (maximum 90 Gy) have not led to further improvements.

**Accuracy of Targeting**

As an imaging-defined procedure without physiological confirmation, the accuracy and precision of focally irradiating the trigeminal nerve was of paramount importance to achieve the desired clinical result. All centers in this study had experience with vascular malformation and tumor radiosurgery and with the surgical management of trigeminal neuralgia. All centers had used both CT and MR imaging for radiosurgery, had performed in-house accuracy testing regarding the reliability of using MR imaging for stereotactic surgery, and had performed ongoing quality assurance tests of the MR imagers used at their institutions.

Previously, we reported on the reliability of 4-mm collimator irradiation of the rat brain and a dose–response relationship for parenchyma. We also tested cranial nerve irradiation in the rat model using the 80% isodose of the 4-mm collimator to irradiate the rat optic chiasm and observed accurate histological effects. In patients, we have used MR-based planning reliably in the management of other small volume targets (such as intracanaliculare acoustic tumors, pituitary microadenomas, and brain metastases) with a 4-mm collimator. Thus, we were confident in its use for the precise irradiation of a cranial nerve (Fig. 3).

**Patient Selection**

Initially, we used radiosurgery as an adjuvant management approach for patients who had undergone prior surgery. However, as good outcomes were identified, we began to offer radiosurgery as the primary approach for patients who declined other surgical strategies. Thus, we were able to stratify results based on the presence or absence of prior surgery. We identified no significant difference in patients who had undergone no prior surgery compared to patients who had had prior surgery. Although all modalities of therapy are limited in their success rate for the “recurrent” trigeminal neuralgia patient, we were encouraged by the response to date of patients who suffered from recurrent pain in this radiosurgery group.

In this study, we found that a maximum dose of 70 Gy was associated with a higher rate of pain relief; further analysis of higher doses is ongoing. The latency to pain relief is variable but usually ranges from 1 to 8 weeks. The reason for this range is unknown. Although histological changes within the nerve at these doses would not be expected before 2 to 3 months, we hypothesize that early pain relief occurs as a result of cessation of ephaptic transmission. Early functional improvement has also been observed after focal irradiation for epilepsy. The delayed and persistent benefit may be achieved after demyelination or injury to the nerve microvasculature. Because the majority of patients maintain facial sensation after radio-

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**Fig. 3.** Axial magnetic resonance images obtained during radiosurgery and 6 months postradiosurgery. a: Image obtained during the procedure showing the isodose plan for trigeminal neuralgia radiosurgery. A maximum dose of 70 Gy was delivered using a single 4-mm isocenter to the left trigeminal nerve. The 10%, 20%, and 50% isodose lines are shown. b: Six months after radiosurgery, a 4-mm diameter region of contrast enhancement is identified in the trigeminal nerve, within the radiosurgical volume (arrowhead).

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surgery and do not develop paresthesia, we believe that any injury caused at this dose range is subtotal, with preserved function of somatic sensory afferents.

As, perhaps, the least invasive procedure for trigeminal neuralgia, we are now continuing to evaluate radiosurgery’s use as a primary treatment for this disorder, especially in elderly patients and those with concomitant medical problems. In this study we identified no significant difference in the response rate between patients with primary or recurrent trigeminal neuralgia, although the number of patients with primary symptoms was small.

Although this report provides results from short-term follow-up experience, we believe this is acceptable because management success is identified early and because potential postradiosurgery complications usually occur by a mean of 12 months. Prior reports of early results after other surgical approaches for trigeminal neuralgia provided the basis for ongoing evaluations of the utility of these techniques. The long-term results after radiosurgery remain to be identified.

Summary

Radiosurgery for trigeminal neuralgia is not new. However, for the first time, we suggest a uniform method for treatment, provide dose-selection guidelines, and posit clinical expectations in different patient subgroups based on our early experience. As a minimally invasive technique with the goal of reducing nerve injury at the root entry zone, radiosurgery does not have the concomitant risks of an open procedure and provides less chance for loss of normal nerve function. Radiosurgery should continue to be evaluated as part of the surgical approach to the management of recurrent trigeminal neuralgia or as a primary procedure for elderly or medically infirm patients.

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References


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