TRIGEMINAL neuralgia, also known as tic douloureux, is a serious health problem with a prevalence of 4 to 5 per 100,000. Patients typically describe severe and sudden facial pain that is like an electric shock. There is growing evidence that one of the causal factors in most patients is compression of the trigeminal nerve root, close to its entry into the pons, by an aberrant arterial or venous loop. Microvascular decompression, first described in the 1950s by Taarnhoj, is used to treat the putative cause by separating the loop from the trigeminal nerve. The pain may be effectively treated by a series of percutaneous techniques (thermocoagulation, microcompression, glycerol injection) that produce a partial lesion of the trigeminal nerve. The concept of stereotactic radiosurgery was first introduced by Lars Leksell who, in 1951, began performing clinical radiosurgery with a stereotactic x-ray beam in patients with essential trigeminal neuralgia. The use of GKS with 201-source cobalt-60 was adopted in 1968. However, due to the efficacy of this tool for the treatment of other diseases, the introduction of the glycerol technique and later of effective drugs for the treatment of trigeminal neuralgia, and, primarily, the absence of high-quality neuroimaging for targeting, GKS for treatment of trigeminal neuralgia was temporarily abandoned. The availability of high-quality three-dimensional MR imaging (for precise targeting of normal structures) and evidence of certain limitations of other techniques prompted a reappraisal of GKS for trigeminal neuralgia during the 1990s. The evidence for safety and efficacy is based on retrospective case studies. However, the evidence supporting the use of other modalities of surgical treatment for trigeminal neuralgia is qualitatively similar. In addition, the numerous studies published to date have not used uniform outcome measures, making comparison between techniques difficult. It must be acknowledged that none of the currently available techniques is perfect, which explains the continuing efforts of neurosurgeons to develop new treatment methods. All of these treatments must be rigorously evaluated in order to know how best to help these patients. The goal of our study is to present the results of a prospective evaluation of the safety and efficacy of GKS in the treatment of trigeminal neuralgia.

Object. Stereotactic radiosurgery is an alternative to conventional surgery for the treatment of trigeminal neuralgia. The authors conducted a prospective evaluation of the safety and efficacy of this method in a large series of patients.

Methods. A total of 100 patients presenting with trigeminal neuralgia were treated and followed up for a minimum of 12 months. The mean age was 68.2 years; 54 patients were male, and 46 were female. Seven had a history of multiple sclerosis, and 42 had already received conventional surgical treatment for trigeminal neuralgia. The intervention consisted of gamma knife surgery to the retrogasserian cisternal portion of the fifth cranial nerve. The median dose used at the maximum was 85 Gy (range 70–90 Gy). The number and intensity of pain attacks were recorded by the patient from 3 months before radiosurgery to a minimum of 12 months after treatment. Before and a minimum of 12 months after treatment, the patient completed a quality-of-life questionnaire. Neurological examination and quantitative sensory testing to evaluate sensory perception were performed by an independent neurologist over this same time period.

At the last visit 83 of 100 patients were reported to be pain free. Fifty-eight of these 83 patients had stopped taking medication during the study. All quality-of-life parameters were improved (p < 0.001). Six patients reported facial paresthesia, and four patients reported hypesthesia. These symptoms were classified as mild. None of the complications reported for other techniques were observed.

Conclusions. Radiosurgery is a safe and effective alternative treatment for trigeminal neuralgia and is associated with a particularly low rate of hypesthesia.

Abbreviations used in this paper: CT = computerized tomography; GKS = gamma knife surgery; MR = magnetic resonance; MVD = microvascular decompression; VAS = visual analog scale.
study was to better define the role of GKS in treatment of drug-resistant trigeminal neuralgia. We relied on very strict methodological rules and took into account recent recommendations, allowing a robust study of outcome and thus facilitating comparability among techniques.

Clinical Material and Methods

The primary objective was to investigate if a single GKS treatment of the cisternal part of the trigeminal nerve root for trigeminal neuralgia resulted in a decrease and/or cessation of pain attacks, compared with before GKS.

The secondary objectives were to estimate changes in intensity of pain attacks, measure the mean number of pain attacks per day, and conduct neurological examinations and quantitative sensory testing for objective evaluation of changes in sensory perception. We also collected data on safety, quality of life, and patient satisfaction.

The study was designed as an open, noncomparative prospective study with a within-subjects design. Ethics committee (CPPRB1) permission was obtained. The study was conducted under the supervision of the health authorities. Any severe adverse event was declared to these authorities. An independent observer who was not part of the study team assessed outcomes.

Patient Population

The diagnosis of trigeminal neuralgia was made according to the definition of the International Headache Society; its definitions of primary and secondary cases and of typical versus atypical were also employed. Before treatment all patients underwent the same routine diagnostic procedures, including MR imaging.

We included patients ranging from 18 to 90 years of age who presented with a clear clinical profile corresponding to trigeminal neuralgia and with a persistent pain level during the previous month (more than one pain attack per day) of a mean intensity higher than 5 of 10 on a VAS, despite optimized drug therapy (or drug therapy limited by dose-related side effects). Other inclusion criteria were a VAS rating on the right side of the scale for satisfaction with current treatment; absence of a visible lesion adjacent to the trigeminal pathways, as demonstrated by MR imaging; provision of a signed informed consent form; and availability of a patient diary completed during the last week before surgery. We excluded patients who had previously been included in this study after presentation with trigeminal neuralgia on the same side, those who had participated in another clinical study within 3 months before presentation for the current study, those who were unable to follow the instructions related to the study, those with a major psychiatric disorder, women of childbearing potential or those who were pregnant, and women who were breast-feeding. Clinical features suggestive of a different diagnosis were of course also exclusion criteria. Before inclusion a pretreatment examination was performed, during which the investigator gave the patient a written description of the study. If the patient decided to participate in the study, he or she then signed an informed consent form.

Gamma Knife Surgery

The procedure on the day of GKS treatment was started with application of the Leksell stereotactic frame (Elekta Instrument AB, Stockholm, Sweden) to the patient’s head after induction of local anesthesia. After the frame fixation, MR and CT imaging were used for dose planning with Leksell GammaPlan (Elekta Instrument AB). The MR images were calibrated before examination and verified by comparison with the CT images for each patient in order to minimize magnetic distortion errors. One single exposure with the 4-mm collimator was placed on the anterior part of the cisternal portion of the trigeminal nerve (Fig. 1). The theoretical aim was to deliver a dose of 90 Gy at the maximal (100%). However, the maximal dose was determined by integrating the measured dose to the brainstem and the age of the patient. Patients with multiple sclerosis were also considered to require a lower dose. Leksell Gamma Knife (Model B, Elekta Instrument AB) treatment proceeded according to routines of the department, and the patients were discharged within 12 hours after radiosurgery. All procedures were performed by the same neurosurgeon.

Data Collection

Data management was based on a case report form on which the following information relevant to the study was recorded before study treatment: study patient number, patient initials, weight, height, age, sex, medical history, and concurrent medication taken within 1 week before inclusion. During the initial visit the investigator reviewed the medical history and the patient diary, in particular asking about the number of pain attacks and the intensity of pain during the week before treatment and during recent months. A series of examinations and evaluations was performed during the week before GKS. The patient was asked to fill out a VAS to measure the general impression of the intensity of pain at baseline and on the occasion of each visit. At follow-up visits, patients were asked about their overall impression of any change in pain level. The incidence of hypesthesia, paresthesia, dysesthesia, and deafferentation pain was recorded. Quality of life was measured with the Epilepsy Surgery Inventory—which was filled in by the neurosurgeon, and the completed data from the case report forms were entered in a computer database. Before entry, each case report form was checked to be sure that the data were complete and reasonable, and then the forms were transferred into a data library of permanent type to avoid unauthorized access.

Before treatment (baseline) and at 1 year an independent neurologist generated data related to safety and efficacy. The case report form data related to the anamnesis; treatment parameters were filled in by the neurosurgeon who performed the radiosurgical procedure.

An independent neurologist—who was not affiliated
Gamma knife surgery for trigeminal neuralgia

with the department organizing the study and not involved in the selection, operation, or clinical treatment of patients included in the study—evaluated the patients before and more than 1 year after GKS. Clinical examination included assessment of corneal reflex, eye examination, skin examination, pinprick test, and sensitivity examination (to assess for hypesthesia). This evaluation included objective pain analysis using a thermal somatosensory device (Medoc 2001 Thermal Sensory Analyser; Medoc Advanced Medical Systems Ltd., Ramat Yishai, Israel), which allowed the determination of somatic sensory perception threshold and quantitative sensory testing. Quantitative thermal and vibratory testing were performed at the site of the pain and on the contralateral side to provide a reference value in all trigeminal divisions bilaterally. Testing of the first division was performed on the forehead above the eyebrow, testing of the second division on the cheek, and testing of the third division just lateral to the mental foramen. Stimuli were applied on the emergence point of each branch to avoid crossing the boundaries of the adjacent territory. Cold sensation, warmth sensation, cold pain, heat pain, and vibratory evaluation (somatic sensory perception threshold test) were determined before GKS and at the last follow up. Warm and cool thresholds as well as hot and cool pain thresholds were determined for each trigeminal division. Starting with a temperature adaptation of 32˚C, ascending and descending ramps of 1˚C/second were delivered. The stimulus was stopped, and there was no access to the data screen until the data were completely collected. Patients underwent an instruction period, followed by three repetitions of the tests, and the scores were then averaged. Measurements were pooled in four groups: 1) affected division, characterized by the presence of the trigger zone (affected); 2) contralateral-mirror image divisions (mirror); 3) unaffected branch (neighbor); and 4) contralateral to affected division adjacent to mirror (contralateral). Results were analyzed by comparing the affected branch with the other trigeminal divisions in each patient (mirror, neighbor, and contralateral branches). These data were subsequently compared with those obtained at the last follow-up visit, with each patient serving as his or her own control. Magnetic resonance imaging was systematically performed in all patients before radiosurgery but was not routinely repeated during the follow-up.

Adverse Events and Patient Withdrawals

An adverse event was considered to be any undesirable clinical event that occurred during the study, whether or not it was considered to be related to the procedure. Adverse events were recorded in the case report form. The adverse events that were observed during the study were followed until they resolved or a reasonable explanation for the event could be given according to the judgment of the investigator.

A patient could be withdrawn if, in the opinion of the investigator, withdrawal was necessary because of medical reasons, a protocol violation, withdrawal of informed consent, or a major technical failure. The reason for withdrawal was clearly described and appropriate patient assessment was performed, preferably according to the final assessment protocol. According to the rules of good clinical practice in clinical trials, only data concerning patients for whom investigation at 1 year was completed were included in the results.

Outcome Measures

Outcome measures used in the analysis were as follows: Class I, pain free without medication; Class II, pain free with medication; Class III, pain frequency reduction superior to 90%; Class IV, pain frequency reduction between 50 and 90%; Class V, no significant reduction in pain frequency; and Class VI, pain worsening.

A recurrence was defined as the change from Class I to a lower outcome class. Thus the situation of a patient who had been pain free without medication (Class I) and who then started taking specific drugs but who remained pain free while taking medication (Class II) was considered a “recurrence.” A minor recurrence was defined as a recurrence that was well tolerated by the patient (because of lower frequency and intensity of the pain) and did not require a proposal for new surgical therapy. A major recurrence was defined as a recurrence that required consideration of further surgery.

Statistical Analysis

The Wilcoxon matched-pairs test was used to analyze the difference between data collected at baseline and the last follow-up visit. Variables were measured over time, and
only one treatment arm was used. No assumption was made about the underlying distribution. Differences between previous surgical treatment categories and the primary efficacy variable were analyzed by using the Mann–Whitney U-test. All tests were two-sided, and the alpha level was 0.05. Multivariate analysis was applied in analyzing data for patients with multiple sclerosis. Nonparametric statistics were used to analyze the VAS data because those data were interpreted as ordinal scaled data.

Results

A total of 110 patients were included in the study, and 100 of these patients were assessable. Assessable patients were those who received GKS, completed all mandatory tests, and were not lost to follow up. One patient died of acute leukemia. The causality was classified as unlikely to be related to the GKS treatment. Two patients underwent additional surgical treatment administered by a surgeon other than the investigator before the first posttreatment study visit. One patient was lost to follow up, and six patients withdrew their consent for participation in the study. Thus, follow-up data were available for 92% of the initially included patients.

All patients were included in the description of demographic characteristics (Table 1). One hundred ten patients were treated (63 male patients and 47 female patients). Their ages ranged from 29 to 90 years (median age 67.5 years). The median duration of the disease was 74 months (mean 111.7 months, range 10–529 months). The side affected was the left in 52 cases and the right in 58 cases. The ophthalmic division (V1) was affected in 22 patients, the maxillary (V2) in 58, and the mandibular (V3) in 62. More than one division was involved in 37 patients (see Table 1). Several patients had currently active or chronic diseases in addition to trigeminal neuralgia. Thirty-three patients had cardiovascular disease, and seven patients had multiple sclerosis. Severe side effects of the drug therapy were reported in 73.6% (81 of 110) of the patients. A vascular lesion in proximity to the trigeminal nerve was clearly demonstrated by preoperative MR images in 56% of the patients.

Before beginning the study, 28 patients had already been treated with thermocoagulation (one–three times), 27 patients had undergone microcompression (one–three times), six patients had undergone surgical MVD, three patients had received treatment with glycerol rhizolysis, and one patient had undergone pars major microsurgical partial section. Sixty-one patients received GKS as a primary treatment (see Table 1).

The median maximal dose was 85 Gy (range 70–90 Gy). The median dose rate was 1.45 Gy/minute (range 1.25–1.65 Gy/minute). The output factor for dose calculation at this time was 0.80. The median gross volume of the portion of trigeminal nerve in the cistern was 64.8 mm³ (range 21.4–148.3 mm³), and its median length in the cistern was 11.6 mm (range 3.3–21.2 mm). The median of the radius of the nerve at the target point was 2.7 mm (range 1.5–4.1 mm) and was usually smaller than the radius of the contralateral nerve (median ratio 0.85, range 0.1–1.4). The median of the average dose to the nerve was 33.6 Gy (range 6–64.6 Gy), and the median of the dose delivered to the plexus triangularis was 28.5 Gy (range 4.4–83.4 Gy). The mean volume of nerve included in the 50% isodose was 30.2 mm³ (range 8–53.5 mm³). The median of the distance between the isocenter and the emergence was 7.84 mm (range 3.4–13 mm). The median of the maximal dose to the brainstem (calculated as the point of the dose–volume histogram corresponding to the 10 mm³ of the brainstem receiving the highest dose; that is, the maximal dose received by more than 10 mm³ of the brainstem) was 1.92 Gy (range 0–16 Gy). No technical failure was encountered.

Initial pain relief occurred in 94% of the patients after a median delay of 10 days (range 0–25 weeks) after GKS (Fig. 2). The mean number of pain attacks during the month before GKS treatment was 46.6 (range 0.86–100), and the mean intensity of these attacks was 8.5 (Fig. 3). The number and intensity of attacks improved overall for the group, with a mean number of attacks during the last month of the study of 0.69 (range 0–100) and a mean intensity of 0.7 (range 0–10). Thirty-four patients (34%) reported pain recurrence 1 to 15 months after initial relief with a median delay of 6 months after GKS (Fig. 2).

Because of treatment failure or insufficient pain relief, 17 patients underwent additional surgical procedures: microcompression in nine patients, thermocoagulation in 11 patients, and MVD in one patient (four of the patients underwent both microcompression and thermocoagulation procedures). All of these patients have been followed for more than 1 year after this new surgery. Seven (42%) of these 17 patients had received surgical treatment between one and four times before inclusion in the study. At the last visit 83 (83%) of 100 patients were reported to be pain free (see Table 2). At the last follow up, patients treated with GKS but no subsequent operation for this condition had a 69% probability of being pain free and a 57% probability of not taking medication for trigeminal neuralgia (see Table 2). Not infrequently, patients who were pain free were reluctant to stop taking their medication completely, due to anxiety about the risk of recurrence.

There was significant (p < 0.001) improvement for all quality-of-life parameters, such as health perception, energy/fatigue, overall quality of life, social function, emotional well-being, cognitive functioning, role limitations, physical functioning, and pain (Fig. 4). Patient satisfaction at last follow up was rated as high in 88% of cases.

The probability of being pain free (see Table 3) at last follow up was lower in patients younger than 60 years of age (66.7% compared with 90.9%, p = 0.01), patients with a distance between the isocenter and the nerve emergence greater than 8 mm (72.7% compared with 88.6%, p = 0.09), and patients with a “trigeminal cistern surface” greater than 39 mm² (72% compared with 89.5%, p = 0.05). A trend toward treatment failure was noted in cases of multiple sclerosis (42.9% compared with 12.8%, p = 0.07) when the nerve minimal dose was lower (5.41 Gy compared with 4.8 Gy). There was an almost significant (p = 0.059) difference in change of number of attacks when the patients with previous surgical treatment were compared with those without. The rate of failure at last follow up was 11.7% in patients who had not had previous operations, compared with 19.5% in patients who had previous operations.

Ten adverse events were reported. These were classified as mild. Six patients reported paresthesia, and four patients reported hypesthesia with no paresthesia. Thus, clinical signs indicating trigeminal nerve injury developed in 10 patients (10%) during the study. Among the four patients
Gamma knife surgery for trigeminal neuralgia

TABLE 1
Clinical characteristics of 110 patients with trigeminal neuralgia who underwent GKS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Cases/Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient age at surgery (yrs)</td>
<td>median 67.5, range 29–90</td>
</tr>
<tr>
<td>male sex</td>
<td>63 (57.3)</td>
</tr>
<tr>
<td>site of op</td>
<td>lt side of face 52 (47.3), rt side of face 58 (52.7)</td>
</tr>
<tr>
<td>patient age at onset of symptoms (yrs)</td>
<td>median 59.5, range 23–88</td>
</tr>
<tr>
<td>preop duration of symptoms (mos)</td>
<td>median 74, range 10–529</td>
</tr>
<tr>
<td>prior drug treatment*</td>
<td>carbamazepine 110 (100), phenytoin 9 (8.2), gabapentine 9 (8.2), baclofen 5 (4.5), others 52 (47.3)</td>
</tr>
<tr>
<td>prior op†</td>
<td>any procedure 49 (44.5), MVD 6 (5.5), thermocoagulation 28 (25.4), balloon microcompression 27 (24.5), glycerol injection 1 (0.9), radiosurgery 0, posterior fossa rhizotomy 1 (0.9)</td>
</tr>
<tr>
<td>distribution of pain‡</td>
<td>V1 only 7 (6.4), V2 only 31 (28.2), V3 only 35 (31.8), V1 and V2 10 (9.1), V2 and V3 22 (20.0), V1, V2, and V3 5 (4.5)</td>
</tr>
<tr>
<td>preop facial numbness</td>
<td>hypesthesia 30 (27.3), paresthesia 41 (37.3), decreased corneal reflex 13 (11.8)</td>
</tr>
</tbody>
</table>

* Other prior drug treatment included valproic acid, clonazepam, lamotrigine, and oxcarbazepine.
† Several patients had undergone more than one type of ablative procedure.
‡ V1, V2, and V3 denote the ophthalmic, maxillary, and mandibular divisions of the trigeminal nerve, respectively.

reporting new hypesthesia, the symptoms partially recovered spontaneously in two patients. Of the six patients who reported paresthesia, two reported both hypesthesia and paresthesia. Among these six patients, paresthesia resolved spontaneously and completely in one patient and partially in three patients. There was no significant change in corneal reflex, eye examination findings, or skin examination findings during the study. None of the patients experienced dry eyes, keratitis, masseter muscle weakness, neuropathic pain, or anesthesia dolorosa. In patients with no clinically identified fifth cranial nerve injury, the objective evaluation of sensory perception by quantitative sensory testing found no significant change of sensitivity threshold on the ipsilateral side (Fig. 5). On the contralateral side the threshold for warm temperature perception was found to be significantly lower at last follow up both for the mirror and contralateral (mirror neighbor) territories (p = 0.001 and p < 0.001, Wilcoxon matched-pairs test). For cold temperature the perception threshold was significantly lower in contralateral territories (p = 0.001), and there was a nonsignificant trend toward a lower perception threshold in the mirror territory (p = 0.09). Individually only 11.6% of these patients presented no change of perception threshold on the contralateral side. No neurological complications outside the trigeminal nerve territory and no systemic complications were reported.

In the analysis of cost efficacy, the time between the date of hospitalization and the date of discharge varied between 1 and 5 days, with the majority of patients (93.7%) staying for 2 days. Only three patients reported having to be absent from work due to GKS treatment. One patient stayed at home for 2 days, one for 5 days, and one for 53 days.

**Discussion**

The first results in the early 1990s regarding GKS treatment for trigeminal neuralgia were very promising, with high rates of pain cessation and very little hypesthesia. Recent papers have reported larger series with longer follow up and certainly more credible results, but, to our knowledge, our study is the first to include a large prospective series and to evaluate the specific questions of the safe-
ty and efficacy of radiosurgery directed toward the cisternal portion of the trigeminal nerve in patients presenting with classic symptoms of trigeminal neuralgia. The only paper demonstrating a high level of evidence to date is that of Flickinger, et al., in which the authors specifically address the question of influence of the irradiated volume of nerve on the clinical outcome.

The reported results for efficacy, delay in response, and risk of recurrence vary considerably between centers. The range of these results has been reported as 35 to 100% for initial pain cessation, 0 to 42% for pain recurrence, and 0 to 57% for trigeminal nerve injury. These differences may well reflect lack of homogeneity in the method of evaluation and the scoring techniques used. Frequently, the rates of complete freedom from pain and of drug cessation are not explicitly indicated. The reported follow-up period is often very heterogeneous, with some studies including data from very short-term follow up in the final analysis. However, several retrospective studies have identified some preoperative and perioperative parameters that appear to influence the outcome significantly. A diagnosis of multiple sclerosis and a history of surgery for the treatment of the trigeminal neuralgia on the same side have both been linked to a lower rate of pain control.

Rare complications have been reported in other series. Matsuda, et al., have reported dry eye in three of 41 refractory cases of trigeminal neuralgia treated with 80 Gy at the dorsal route entry zone target. These three patients reported dry eye with diminution or absence of corneal reflex, but no other abnormality of the cornea and conjunctiva was revealed by ophthalmological examination. In these three patients, hypesthesia of the first division of the trigeminal nerve area had been found before their dry eye symptoms appeared. These authors have demonstrated that the incidence of this complication was significantly related to irradiated volume of brainstem. Maher, et al., conducted MVD and reported focal changes consistent with atheromatosis in two adjacent veins and the superior cerebellar artery. The patient had undergone radiosurgery 10 months pre-

### TABLE 2

<table>
<thead>
<tr>
<th>Patients w/ No Repeated</th>
<th>Patients w/ Repeated</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients w/ Repeated Surgery After GKS†</td>
<td>Patients w/ Repeated Surgery After GKS</td>
<td>All Patients</td>
</tr>
<tr>
<td>no. of patients</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>outcome class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, no pain &amp; no medication</td>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>II, no pain w/ medication</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>III, pain frequency reduction &gt;90%</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>IV, pain frequency reduction 50–90%</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>V, no pain reduction</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>VI, pain worsening</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Data reported for patients with a minimum of 12 months of follow up. † At last follow up, patients with no repeated surgery after GKS had a 69% probability of being pain free.
Gamma knife surgery for trigeminal neuralgia

Previously, following a failed balloon microcompression, thus making it difficult to ascertain whether either of the two procedures was responsible for the complication. However, patients should be carefully observed for possible delayed ischemic events secondary to radiation-induced vascular injury\textsuperscript{16,36} after any surgical procedure in trigeminal neuralgia.

Quality of life was significantly improved at the last follow up, particularly in patients with good pain control. This finding is consistent with previous reports.\textsuperscript{46} Patient satisfaction was reported to be high, with the majority considering their treatment as successful.

However, contrary to some previously published studies,\textsuperscript{35,48} the sex of the patient, the laterality of the neuralgia, the territory of the pain, and the presence of preoperative hypesthesia did not significantly influence the probability of pain cessation in the present series.

According to Flickinger, et al.,\textsuperscript{10} improved pain relief was correlated with younger age ($p = 0.025$) and fewer prior procedures ($p = 0.039$). However, our results contradict

![Graph depicting three quality-of-life composite scores for 65 patients with trigeminal neuralgia who completed the Epilepsy Surgery Inventory–55 before GKS and at follow up after GKS.](image)

**TABLE 3**

Treatment factors in 83 patients with and 17 patients without successful GKS treatment of pain associated with trigeminal neuralgia and in 90 patients without and 10 patients with clinical signs indicating trigeminal nerve injury during the study*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients w/ Successful Treatment</th>
<th>Patients w/ Failed Treatment</th>
<th>p Value</th>
<th>Patients w/o Nerve Injury</th>
<th>Patients w/ Nerve Injury</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient age at surgery (yrs)</td>
<td></td>
<td></td>
<td>0.012</td>
<td>0.812</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>73.9</td>
<td>58.9</td>
<td></td>
<td>70.7</td>
<td>69.2</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>30–98</td>
<td>45–87</td>
<td></td>
<td>30–89</td>
<td>54–82</td>
<td></td>
</tr>
<tr>
<td>dose max (Gy)</td>
<td></td>
<td></td>
<td>0.318</td>
<td>0.161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>87.5</td>
<td>80</td>
<td></td>
<td>85</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>range</td>
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<td>70–90</td>
<td></td>
<td>70–90</td>
<td>80–90</td>
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<tr>
<td>nerve mean dose (Gy)</td>
<td></td>
<td></td>
<td>0.793</td>
<td>0.849</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>33.1</td>
<td>30.4</td>
<td></td>
<td>32.8</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>6–64</td>
<td>12–65</td>
<td></td>
<td>6–65</td>
<td>20–55</td>
<td></td>
</tr>
<tr>
<td>nerve min dose (Gy)</td>
<td></td>
<td></td>
<td>0.103</td>
<td>0.496</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>5.4</td>
<td>4.8</td>
<td></td>
<td>5.4</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>2–17</td>
<td>0–8.5</td>
<td></td>
<td>0–16.8</td>
<td>3–8</td>
<td></td>
</tr>
<tr>
<td>vol of trigeminal nerve in 50% isodose (mm$^3$)</td>
<td></td>
<td></td>
<td>0.129</td>
<td>0.356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>29.8</td>
<td>32.9</td>
<td></td>
<td>31</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>11–54</td>
<td>13–44</td>
<td></td>
<td>13–54</td>
<td>11–37</td>
<td></td>
</tr>
<tr>
<td>mean dose to brainstem (Gy)*</td>
<td></td>
<td></td>
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<tr>
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<td>8–12.5</td>
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* Maximal dose received by more than 10 mm$^3$ of the brainstem.
† Distance between the isocenter and the emergence of the nerve.
these findings, showing a lesser probability of pain cessation in patients younger than 60 years of age.

Prior surgical procedure (regardless of the technique used) was correlated in our series with a lower rate of efficacy of radiosurgery, as in the majority of previous studies.\textsuperscript{10,35,48} In our series the probability of freedom from pain at 1 year in patients without previous surgery and in patients with one, two, or three or more previous surgical interventions was 88.3, 81.8, 80, and 75\%, respectively.

The rate of trigeminal nerve injury, as estimated by patient reports, clinical examination, and quantitative sensory testing, was low in our series.

Quantitative sensory testing allows the evaluation of unmyelinated (C) and small-caliber myelinated (A\textsubscript{6}) fibers.\textsuperscript{64,67} Abnormal findings in quantitative sensory testing have been previously demonstrated in trigeminal neuralgia, with raised warm and tactile thresholds in those divisions affected by trigeminal neuralgia; an elevation of warm, hot, pain, and two-point discrimination thresholds may also be found in adjacent branches.\textsuperscript{44} Sinay and colleagues\textsuperscript{59} have found quantitative sensory testing abnormalities (cold and warm hypesthesia and high cold and heat pain thresholds) in nine patients with trigeminal neuralgia, compared with 10 healthy individuals; these changes occurred in the symptomatic division and adjacent branches and were also demonstrated on the contralateral side in a minor form. Our data suggest that the contralateral sensory dysfunction tends to resolve after radiosurgery. Quantitative sensory testing allowed us to test a wide spectrum of cutaneous modality thresholds in our population and to compare the results before and 1 year after radiosurgery. Contrary to what is often observed with other physical techniques that include an ablative mechanism, the majority of patients with prolonged pain cessation after GKS had absolutely no sign of trigeminal injury on follow-up testing.

A correlation between hypesthesia and pain response does, however, exist. Rogers and associates\textsuperscript{53} have reported a higher probability of pain cessation in patients experiencing trigeminal injury after radiosurgery. We failed to find this significant correlation, but it is interesting to note that 100\% of the patients experiencing hypesthesia after GKS in our series were cured. Maesawa, et al.,\textsuperscript{35} found that the absence of preoperative sensory disturbance or previous surgery correlated significantly with complete or partial pain relief over time. Pollock, et al.,\textsuperscript{47} in a comparison of two dose regimens (70 and 90 Gy), have found that higher doses of radiation correlated with better facial pain outcomes but also with a higher incidence of trigeminal nerve dysfunction when posterior targets were used. In our series, high doses (median 85 Gy) were associated with a high probability of pain cessation but a low rate of trigeminal nerve injury when more anterior targets were used (7.5 mm

**Fig. 5.** Graphs depicting objective evaluation of sensory perception by quantitative sensory testing before GKS and at a minimum of 12 months after GKS. The thresholds for temperature warm, temperature cold, pain warm, and pain cold were evaluated in the territory of the pain (affected), the neighboring territory (neighbor), the contralateral territory symmetrical to the affected territory (mirror), and the contralateral territory(ies) neighboring the “mirror” territory (contralateral). Statistically significant differences are indicated with an asterisk.
from the emergence of the nerve, instead of the 2 mm used in the series reported by Pollock, et al."

Other studies have shown a high correlation between the dose delivered to the brainstem and the probability of trigeminal nerve dysfunction, as assessed by incidence of facial numbness.13,38 This major factor perhaps explains why, in series using high doses (80–90 Gy) but an anterior target57 and in the present series, the efficacy is similar but trigeminal nerve dysfunction seems much less frequent and less severe, compared with those in series using high doses and a more posterior target.47

In addition, the complication of dry eye syndrome reported by Matsuda, et al.38 did not occur in our series. These authors used a posterior target and correlated this complication with the delivery of high doses to the brainstem.13,38

The distance from the isocenter to the emergence of the nerve proved in our series to be optimal around 7.5 mm (median of 7.5 mm for the group with successful treatment versus 8.67 mm for the group with failed treatment). This finding is in keeping with the recommended minimal distance of 5 mm and optimal distance of 8 mm in a retrospective study of 47 patients by Massager, et al.37 Others have emphasized the fact that the dorsal root entry or exit zone can be variable in length, particularly in the case of the trigeminal nerve, and may extend to a more distal portion of the nerve than previously described.39 The variability of the limit between the schwannian and glial environment of the nerve as it exits the brainstem, classically located 3 mm from the emergence, must be borne in mind.9 In our series the success rates were 72.7, 84, and 96.6% when the distance between the isocenter and the emergence of the nerve at the brainstem was, respectively, more than 9 mm, between 9 and 7 mm, and less than 7 mm. Unfortunately, the closer the isocenter is to the brainstem, the higher the risk of hypesthesia. Consequently the strategy in our group is to try to position the isocenter approximately 7 mm from the emergence for safe use of maximal doses for efficacy (80–90 Gy).

The nerve length included in the 50% isodose line was not correlated in this study with efficacy or with the incidence of trigeminal nerve dysfunction. Flickinger, et al.,36 in a prospective randomized study (44 patients given one-dose delivery and 43 patients given two-dose delivery) similarly reported the absence of benefit when the volume of the nerve was increased and even suggested a higher probability of complications. These results have been confirmed by other authors.18 Similarly, Massager, et al.37 using the anterior target and a slightly higher dose (median 90 Gy instead of the median of 85 Gy used in our series) significantly increased the nerve length included in the 50% isodose by using source plugging, which was associated with an elevated rate of trigeminal nerve injury (38%, compared with the 10% found in our series).

In cases in which high maximal doses (80–90 Gy) are used instead of lower doses (70 Gy), several authors have demonstrated a significant improvement in the rate of pain cessation and a reduction of recurrence rate.23 It is possible that radiosurgery directed to a more anterior portion of the cisternal nerve may allow safe use of higher doses by reducing the risk of sensory loss.

The presence of vascular conflict, revealed by preoperative high-resolution MR imaging, was found by Brisman, et al.,9 to correlate with better outcome in patients who had not previously undergone surgery. We did not find such a difference in our series. The probability of pain freedom at last follow up for the 60 patients presenting with and the 40 patients presenting without a clear neurovascular conflict demonstrated on MR imaging was 83.3 and 87.5%, respectively (p = 0.78).

Multiple sclerosis in patients presenting with trigeminal neuralgia has been reported to be associated with a lower rate of successful treatment.15,54 However, due to the particular difficulties related to this condition when using other surgical techniques, several authors have suggested that radiosurgery provides an acceptable safety/efficacy ratio in such patients. In our series, the seven patients with multiple sclerosis had a 57.1% probability of pain cessation, compared with 87.2% for the 94 patients without multiple sclerosis. However, this difference did not reach statistical significance (p = 0.07), perhaps because of the relatively small number of patients with this condition in our series. In a group of seven patients with multiple sclerosis treated with GKS using a posterior target and high doses (80–90 Gy), Huang and colleagues15 found a high incidence of facial numbness (57%) and a longer delay until pain cessation (from 1 day to 8 months). In line with these results, and based on the assumption that patients with multiple sclerosis are often more sensitive to any surgical intervention, any patient with the condition in our series was systematically subjected to a lower dose (the median of the maximal dose of 80 Gy), which perhaps explains the lower incidence of pain cessation for this group.15

Surgical methods for the treatment of trigeminal neuralgia can be separated into two groups. Ablative techniques (thermocoagulation, balloon microcompression, and glycerol injection) are usually performed percutaneously after a brief induction of general anesthesia. They have in common a very high rate of trigeminal nerve dysfunction (including keratitis in the V1 territory), but they are simple techniques that are easy to repeat and readily suitable for use in elderly patients.32 Microvascular decompression is established as the technique of choice and has the major advantage of treating the probable cause of the disease as well as offering a very low risk of subsequent trigeminal nerve dysfunction.23,36 This procedure is performed using craniotomy after induction of general anesthesia. Perioperative death is rare, oculomotor deficits are usually transient, and the incidence of facial palsy and deafness is reasonably low.23,36 Radiosurgery has the advantage of being the least invasive available procedure and is performed with local anesthesia. In addition, the rate of trigeminal dysfunction is remarkably low with radiosurgery and is comparable to that occurring with MVD. It is intriguing to consider the rarity of clinical injury to the trigeminal nerve, despite a high rate of pain cessation. With percutaneous treatment, and particularly with thermocoagulation, the induction of hypesthesia is essentially mandatory for prolonged pain cessation.57 With radiosurgery, the majority of patients experience the disappearance of trigeminal neuralgia without sustaining any trigeminal nerve dysfunction (even if the appearance of posttreatment hypesthesia does increase the probability of pain cessation). This evidence is rather surprising in terms of the physiopathology of the effect, but it clearly points to an advantage of radiosurgery over percutaneous techniques.

Radiosurgery as a first-line treatment is frequently suggested in everyday practice for patients with trigeminal neu-
ropathy, including patients who are good candidates for MVD.\textsuperscript{26} Even if some authors use the good safety/efficacy ratio of radiosurgery as an argument for promoting this treatment as a first-line alternative to conventional methods,\textsuperscript{27} we still recommend MVD in young patients, as this technique remains, in our opinion, the gold standard treatment for this group. In young patients who decline MVD, radiosurgery may be offered on the grounds that it is associated with a very low rate of numbness for a similar rate of efficacy, compared with percutaneous methods. However, the exact indications for radiosurgery are still a matter of controversy. Only prospective randomized controlled trials comparing each of the alternative methods to the gold standard (MVD) are likely to clarify this issue.

A cautious review of the literature shows a huge heterogeneity in surgical practice. Local practice, practitioner skill level, and availability of technical capability greatly influence the form of treatment offered. In our center, all the main techniques (MVD, thermocoagulation, balloon microcompression, and radiosurgery) are available and currently practiced; we believe that this range of treatments diminishes bias in optimal treatment choice for an individual patient at a particular moment in his or her medical history.

To our knowledge, our study—a large prospective, controlled cohort study with a within-subject design in which an independent observer assessed outcomes—is unique in the current literature. Earlier papers have reported standard follow up of a cohort of patients evaluated prospectively,\textsuperscript{43,49} and the study by Flickinger and associates\textsuperscript{10} addressed a specific technical issue (a two-isocenter protocol versus a one-isocenter protocol). In our study, the independent assessment was performed by a neurologist with extensive expertise in facial pain but with no direct professional or personal relationship with the neurosurgeons in charge of radiosurgery or with the study sponsor. This neurologist has received no direct benefit from this study. To our knowledge, this study is the first to address the safety and efficacy of radiosurgery in trigeminal neuralgia on the basis of high-quality evidence. The only side effect and/or complication caused by GKS observed in this trial was hypesthesia in 10 patients (10%), in whom clinical signs indicating trigeminal nerve injury developed. This rate is very low, compared with the rates published in the literature with percutaneous operations, and comparable to that reported with MVD.\textsuperscript{16} The main methodological limitation of this study was the length of the follow up.

Conclusions

In this study we have demonstrated that radiosurgery can reduce or eliminate pain attacks in patients with trigeminal neuralgia. This study demonstrates that GKS applied to the retrogasserian part of the trigeminal nerve in its cisternal portion can alleviate essential trigeminal neuralgia. Radiosurgery is the least invasive surgical technique for the treatment of trigeminal neuralgia. Rates of pain control and pain recurrence appear to be in line with ablative techniques. The delay of pain cessation is longer than with the other techniques. The rate of hypesthesia is very low and rarely troublesome. None of the complications described with the other techniques were observed in this study. This study establishes GKS as a safe and effective treatment of trigeminal neuralgia. Neurovascular decompression is classically considered to provide the best rate of long-term complete pain relief and preservation of facial sensation. To further refine the role of GKS, compared with other techniques, a randomized controlled comparative study fulfilling stringent quality criteria is required.\textsuperscript{11} Microvascular decompression, however, should still be considered as first-line treatment for trigeminal neuralgia.

Disclosure

This study was supported by Timone University Hospital (Assistance Publique des Hôpitaux de Marseille) and by Elekta Instrument AB, Stockholm, Sweden.

Acknowledgments

We thank Dr. Aileen McGonigal for help with the English-language editing, and Dr. J. Gouriet for statistical work.

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Manuscript received February 28, 2005. Accepted in final form December 12, 2005.
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