Gamma Knife Surgery for Trigeminal Neuralgia: Outcomes and Prognostic Factors

Jason Sheehan, MD, PhD, Hung-Chuan Pan, MD,

Matei Stroila, PhD, Ladislau Steiner, MD, PhD

Lars Leksell Center for Gamma Surgery

Department of Neurological Surgery

University of Virginia

Charlottesville, VA 22908

Corresponding Author:

Jason Sheehan

Box 800-212

Department of Neurological Surgery

Health Sciences Center

Charlottesville, VA 22908 USA

Voice: (434) 982-1454

FAX: (434) 982-0543

E-mail: jps2f@virginia.edu

Abstract

Purpose: Microvascular decompression and percutaneous ablation surgery have historically been the treatments of choice for medical refractory trigeminal neuralgia (TGN). Gamma Knife surgery has been utilized as an alternative, minimally invasive treatment in trigeminal neuralgia. In the present study, we evaluate the long-term results of Gamma surgery for the treatment of trigeminal neuralgia.

Materials and Methods: From 1996 to 2003, we treated 151 cases of trigeminal neuralgia with Gamma Knife surgery. In this group, radiosurgery was performed once in 136 patients, twice in 14 patients, and three times in one patient. The types of trigeminal neuralgia were as follows: 122 patients with typical TGN; 3 with atypical TGN; 4 with multiple sclerosis associated TGN; and 7 patients with TGN and a history of a cavernous sinus tumor. In each case, the radiosurgical target was chosen 2 to 4 mm anterior to the entry of the trigeminal nerve into the pons. The maximum doses ranged from 50 to 90 Gy. The median age of the patients was 68 (range 22-90) years old, and the median time from diagnosis to Gamma surgery was 72 months (range 1 to 276 months). The median follow-up was 19 (range 2 to 96) months. Clinical outcomes and post-radiosurgical MR imaging studies were analyzed. Univariate and multivariate analyses were performed to evaluate factors that correlated with a favorable, pain-free outcome.

Results: The mean time to relief of pain was 24 (range 1-180) days. The percentage of patients who were pain-free without medication at 1, 2, and 3 years follow up was 47%, 45%, and 34%, respectively. The percentage of patients who experienced some degree of improvement in their pain was 90%, 77%, and 70% at 1, 2 and 3 years follow-up, respectively. Thirty-three of 122 (27%) patients with initial improvement later experienced pain recurrence at a median time of 12 months post-radiosurgery (range 2-34 months). Among those with recurrence of their symptoms, 14 patients received additional Gamma surgery, 6 had a microvascular decompression, 4 had a glycerol injection, and 1 patient had a percutaneous radiofrequency rhizotomy. Twelve (9%) patients developed the onset of new facial numbness post-radiosurgery. Post-radiosurgical MR imaging changes were noted in 9 patients (7%). In univariate analysis, right-sided neuralgia (p=0.0002) and a previous neurectomy (p=0.04) correlated with a pain free outcome; in multivariate analysis, both right-sided neuralgia (p=0.032) and age (p=0.05) were statistically significant. New onset of facial numbness following Gamma surgery correlated with more than one Gamma surgery (p=0.002).

Conclusion: At last follow-up, Gamma Knife surgery effectuated pain relief in 44%. Some degree of pain improvement at 3 years post radiosurgery was noted in 70% of patients with trigeminal neuralgia. Although less effective than microvascular decompression, radiosurgery remains a reasonable treatment option for those unwilling or unable to undergo more invasive surgical approaches and offers a low risk of side effects.

Key words: trigeminal neuralgia, Gamma Knife, radiosurgery, facial pain, tic douloureux

Introduction

Trigeminal neuralgia (TGN) is a paroxysmal lancinating pain confined to a distribution encompassing one or more of the branches of the trigeminal nerve on one side of the face. It frequently arises in conjunction with a vascular contact between an artery or vein and the trigeminal nerve at the root entry zone (REZ). This fact led to the hypothesis of a causal relationship between vessel compression and trigeminal neuralgia and the devising of microvascular decompression surgery.[2,9,10,16] First line treatment for patients with TGN is medical therapy. However, many patients with this condition eventually fail medical therapy because of refractory pain or intolerable medication side-effects. More invasive treatment options include microvascular decompression (MVD), and neuronal modulating procedures such as glycerol rhizolysis, radiofrequency rhizotomy, percutaneous balloon microcompression, and peripheral nerve blocks.[2,8,9,35,36]

In 1953, radiosurgery with X-rays was first utilized to treat TGN, and the long-term success (greater than 17 years) of two patients following radiosurgery was first reported in 1971.[21] Since then, radiosurgery has been employed to treat TGN. Radiosurgery has been viewed as a minimally invasive treatment option with few side effects. In various series, pain free outcomes have ranged from 21.8% to 75%, and complication rates varied from 2.7% to 37%.[3,4,17,18,20,28,30,31,37,38] However, questions remain about the efficacy, safety, and durability of Gamma surgery for TGN. In an effort to answer some of these questions, we report on our experience with Gamma Knife surgery for the treatment of 136 patients with trigeminal neuralgia and atypical facial pain and analyze the factors associated with a pain free outcome.

Methods

Patient Population

At the University of Virginia, a retrospective review of a prospectively created database was performed to analyze patients treated with Gamma Knife surgery for facial pain. From 1996 until 2004, a total of 136 patients were treated, and 122 had a diagnosis of trigeminal neuralgia while 14 had a diagnosis of atypical facial pain (Table 1). Ninety-four patients had right sided pain while 42 patients had left sided pain. The distribution of pain in the divisions of the trigeminal nerve was as follows: V1= 6.9% of patients; V2= 28.4%; V3= 23.3%; V1 and V2= 15.5%; V2 and V3= 15.5%; and V1 and V2 and V3= 11.2%. Pre-operative facial numbness was noted in 34 patients (25%).

This patient population consisted of 66 males and 70 females. The mean age was 68 years. The vast majority of the patients had at some point been treated with more than one pharmacological agent, and all patients were refractory to medical treatment. In addition, seventy-four patients had undergone previous surgical procedures for treatment of their facial pain. Twenty–three (17%) underwent MVD, 46 (34%) had glycerol injections, 2 (1.5%) had radiofrequency rhizotomies, and 32 (24%) had neurectomies.

The median follow-up was 19 months. The number of patients with 1 year, 2 years, and 3 years follow-up were 118, 64, and 39, respectively. Those patients who experienced a lack of treatment response or early pain recurrence were considered Gamma Knife surgery failures. Patients who initially had a favorable response but later experienced recurrence of their pain were considered for repeat radiosurgery.

Radiosurgical Technique

A total of 151 Gamma surgeries were performed on these 136 patients with 14 undergoing a second Gamma surgery and one undergoing three Gamma surgeries. Radiosurgery was performed using the Model U (1989 to June 2001) and Model C (July 2001 to present) Gamma Knifes (Elekta Instruments, Norcross, GA). The Leksell model G head frame was applied in the main operating room under local anesthesia with light intravenous sedation (typically propofol or fentanyl and versed). Most patients were treated with one isocenter (median 1, range 1 to 7) delivered with the 4mm collimator helmet.

Maximal doses ranged from 50 to 90 Gy, and the median dose was 80 Gy. The maximum prescription doses were as follows: 50 Gy in 0.7% of procedures; 60 Gy in 0.7%; 70 Gy in 43%; 80 Gy in 55%; and 90 Gy in 0.7% of cases. In each case, the root entry zone (REZ) was encompassed within the treatment plan to allow a low dose of radiation (approximately 20 to 30 Gy) to the edge of the pons. The doses less than 70 Gy were only given at retreatment. The center of the targeting was typically chosen 2 to 4 mm anterior from the junction of the trigeminal nerve and the pons. Targets were categorized into two groups. The first group of targets is when the trigeminal nerve was covered with the 50% isodose outside of the brainstem (Figure 1). The second category of targets was when the 50% isodose curve was adjacent to the surface of the brainstem (Figure 2). Fifty-two percent of patients were treated using the first target strategy and forty-three percent were treated using the second strategy. Five percent of patients had 4-mm isocenters used to cover the entire portion of the trigeminal nerve on the affected side. All Gamma plans were developed by the senior author (L.S.).

Imaging Techniques

The trigeminal nerve was typically imaged using a 1.5 Tesla MRI unit (GE Medical Systems, Milwaukee, WI). Localization was performed using T1-weighted and fast spin echo T2-weighted axial images along with coronal images of the nerve. The axial volume acquisition of 512x216 matrices was divided into sections of 1 mm without gaps. T1 weighted images were also repeated after administration of gadolinium. Two patients underwent computed tomography (CT) for targeting because of medical conditions (e.g. a pacemaker) that prohibited MR imaging. However, CT is not ideal for targeting purposes.

Patient Follow-up

Clinical Follow-up of Patients

Patients received direct clinical follow-up every 3 to 6 months. If the patient failed to make his clinical appointment, a questionnaire was sent to the patient. On that questionnaire, patients were asked to assess their pain intensity, time to onset of pain relief, presence or absence of facial numbness, pharmacological agents taken for pain, and whether they underwent additional surgical interventions for treatment of facial pain. Patients were specifically asked if they were pain free or had improvements in their pain following Gamma surgery. They were also asked about the presence of new or worsened facial numbness post-operatively.

Imaging Follow-up of Patients

Patients received routine MRI examinations 6 to 9 months after Gamma surgery. T1-weighted sequences with and without contrast and T2-weighted images were performed to evaluate for any adverse consequences. If a patient developed the onset of new facial numbness post-radiosurgery, that patient underwent additional MRI testing at the time of the onset of the numbness to evaluate for any brain tissue changes.

Statistical Analysis

Descriptive statistics were computed using standard methods to calculate median or mean. Univariate and multivariate analysis were performed to assess for variables that were predictive of a pain free outcome after Gamma surgery. The following variables were assessed: right sidedness of the pain; typical or atypical pain; age; gender; number of isocenters; target distance from nerve root entry zone (either the 50% isodose well outside of or adjacent to the brainstem); maximal dose; presence of post-GK imaging changes; presence of previous interventions; a previous MVD; previous glycerol injection; previous neurectomy; increasing length of time from diagnosis to Gamma surgery; distribution of the pain; the presence of pre-operative facial numbness; the presence of post-operative facial numbness; and recurrence of pain in those patients who were treated more than once with Gamma surgery. The unpaired Student's t-test or analysis of variance were used for continuous variables. Nominal or ordinal data was compared using the two-tailed Fisher's exact test. All statistical analyses were conducted with the aid of Statview 5.01 (SAS Institute, Cary, NC). Statistical significance was defined as a p less than or equal to 0.05.

Results

Clinical Outcome

Median follow-up in the 136 patients was 19 months. The median interval from the treatment to symptom improvement was 24 (range 1-180) days. Few patients experienced a benefit more than 2 months following radiosurgery. At the last time of follow-up, 44% of patients were pain free without medication, and 56% still had some degree of pain (Table 2). The percentage of patients who were pain free without medication at specific time points was as follows: 47% at 1 year (n=118 patients); 45% at 2 years (n=64 patients); and 34% at 3 years (n=39 patients). In a similar fashion, those who experienced some improvement in pain post-radiosurgery were as follows: 90% at 1 year (n=118 patients); 77% at 2 years (n=64 patients); and 70% at 3 years (n=39 patients). Forty-six percent of those with typical TN (n=122) were pain free at last follow-up whereas only 29% of those with atypical TN (n=14) were pain free (p=0.35, t-test).

In the follow-up, 33 patients had recurrence of their pain after some initial relief. The median time to recurrence of facial pain was 12 months. Among those patients with recurrence of pain, 14 patients underwent an additional Gamma surgery, 6 patients had a microvascular decompression, 4 patients a glycerol injection, 1 patient a radiofrequency rhizotomy, and 5 patients refused any further treatment.

Factors Statistically Associated with a Pain Free Outcome

Following Gamma Knife surgery, pain relief was monitored by serial physician's assessments at approximately 3 month intervals. Most patients experienced pain relief within the first two months following Gamma Knife surgery. However, the pain relief was not always lasting.

In order to evaluate the efficacy of Gamma surgery in a rigorous fashion, we chose to consider factors that were statistically related to a pain free outcome at the last time of follow-up. Seventeen factors in all were tested (Table 3). In univariate analysis, right sidedness to the pain ($p=0.0002$) and a previous neurectomy ($p=0.04$) were statistically related to a pain free result. In multivariate analysis, again right sidedness ($p=0.032$), and this time increasing age ($p=0.05$) were related to a pain free result. No other factors were significantly related (i.e. $p>0.05$) to a pain free result following Gamma surgery.

Clinical Complications

Twelve patients (9%) experienced new post-operative numbness following Gamma surgery (Table 1). In our study, 4 patients out of 14 who had repeat Gamma surgery (29%) had new facial numbness. Eight out of 122 patients who had only one Gamma surgery (7%) developed new facial numbness. There was a statistically significant difference in the incidence of new facial numbness in these two group ($p=0.002$, t-test). We were unable to establish a significant relationship between radiation dose and post-operative facial numbness. No patient experienced the new onset of corneal reflex loss or anesthesia dolorosa.

A total of 26 patients had either new or worsened facial numbness after Gamma surgery. The severity of the numbness was as follows: 12 patients with mild numbness; 10 with somewhat disturbing numbness; and 4 with severe numbness. Twenty-one of 122 patients (17%) receiving only one Gamma surgery developed new or worsened facial numbness while 5 out of 14 patients (36%) receiving more than one Gamma surgery experienced new or worsened symptoms. The difference was not statistically significant (p=0.14, T-test). In addition, 12 of 46 patients (26%) with a history of glycerol injection experienced new or worsened facial numbness as compared to 14 out of 90 patients (16%) without a history of glycerol injection (p=0.14, T-test). One patient out of all those treated reported new onset of facial numbness post Gamma surgery that she felt was worse than her trigeminal neuralgia itself. This patient experienced numbness that led to excessive drooling, but she did not have anesthesia dolorosa.

Imaging Outcome

Nine patients (6.6%) had post-radiosurgical imaging changes including focal contrast enhancement or focal T2-weighted signal change (Figure 3). Among those nine patients who had post-operative imaging changes, 4 had no numbness, 3 had mild numbness, and 2 had severe numbness.

Discussion

Rationale for Using the Gamma Knife to Treat Trigeminal Neuralgia

The underlying etiology of trigeminal neuralgia has been the subject of intense investigation for more than a century. Research by Pfluger (1859) and Heidenhain (1861) demonstrated that the proximal end of a nerve was more excitable than the distal end and that the excitability of the nerve increased near the region of a cross section.[13] Adrian (1930) and Skoglund (1942) discovered that sections of sensory nerves are more efficient impulse generators than their motor counterparts.[1,33] As early as 1941, Olivecrona understood and described that mechanical pressure along the root or at the level of the ganglion could be the cause of trigeminal neuralgia.[25] In pioneering work, Granit, Leksell, and Skoglund (1944) demonstrated that local pressure on nerve fibers could result in painful afferent discharges from the injured neural segment.[11] More recently, Jannetta and others have suggested that vascular compression of the trigeminal nerve may be a causal agent in trigeminal neuralgia.[2,9,23] Despite such hypotheses, the fact that balloon compression of the nerve can lead to symptomatic improvement in some patients underscores the true lack of understanding as to the underlying pathophysiology of trigeminal neuralgia.[7]

With the development of the Gamma Knife and a limited understanding of the neurophysiology of pain, Dr. Leksell was obsessively interested in the treatment of patients with intractable pain.[14,17,21,34] In his book Brain Fragments, Dr. Leskell wrote, "One can accept death, but one cannot accept the deep, devastating pain. Sharp, intractable pain is like hell 'without escape, without hope and without Heliotrope when Venom burns.' Standing at the bedside without ever having experienced pain, it is impossible to imagine the patient's agony, and it is impossible to understand that a short time without pain can be extreme happiness."[22] As soon as he developed a new technique, Leksell would try it in the management of both intractable pain and tic douloureux.[21, 22] With the Gamma Knife unit installed in Stockholm, he asked Dr. Hakanson to find the 2 patients treated with orthovoltage for their trigeminal neuralgia. Following the successful long-term outcome of these 2 patients, Dr. Leksell and Dr. Hakanson treated 48 patients between 1970 and 1978, and follow-up information was available on 46 of these patients (Personal communication, Sten Hakanson, 2004).[21] In the first 24 patients, plain stereotactic skull X-rays were used for targeting, and 33% were pain free at 6 months while only 8.3% were pain free at a mean follow up of 26 months (Personal communication, Sten Hakanson, 2004). In the second set of 22 patients, the position of the Gasserian ganglion was determined by transoval cisternography using tantalum dust. For that group, the percentages of patients who were pain free at 6 and 26 months were 59% and 18%, respectively (Personal communication, Sten Hakanson, 2004).

However, after an initial flurry of activity by Drs. Leksell and Hakanson, the use of the Gamma Knife to treat trigeminal neuralgia nearly vanished until Dr. Rand began to use and then reported satisfactory results in trigeminal neuralgia patients with Gamma surgery.[29] Some of this lull in activity was due to the difficulty with targeting, and this problem was surmounted with the advent of MRI. Another cause for the resurgence of interest in the Gamma Knife was the change in the target from that of the Gasserian ganglion to the REZ. Following Dr. Rand's report, some advocated that radiosurgery would replace microvascular decompression.[38] Major series have reported pain free results of 21.8% to 75% and improvement in pain of 65% to 88% following Gamma surgery (Table 4). Most of these studies note that dose, history of previous surgery, and radiographic evidence of vascular compression to the trigeminal nerve were statistically related to a more favorable outcome. However, considering the complication rates of 2.7% to 37% in these series, only the results reported by Dr. Young (1998) would seem to be comparable to those from large microvascular decompression series (Table 4).[38]

Overall, the treatment of choice for trigeminal neuralgia remains microvascular decompression. However, for patients who are ineligible for or unwilling to undergo more invasive neurosurgical procedures, Gamma surgery offers a reasonable alternative. Gamma surgery also does not carry the same type and degree of risks that microvascular decompression does. For instance, in a long-term series of microvascular decompression patients, there were the following risks from the series by Dr. Jannetta: 0.2% death; 0.1% brain stem infarct; and 1% hearing loss.[2] None of these complications were observed in our series nor were they associated with radiosurgical treatment of trigeminal neuralgia in other major centers. Ultimately, the patient must choose the type of intervention he or she is willing to undergo.

Problems with comparing treatment modalities for trigeminal neuralgia

Although the end point of pain relief is the same in most studies, the patient population between microsurgical and radiosurgical studies is often times quite different. Many patients who are referred for Gamma surgery are older, have had prior surgeries with little or no benefit, possess many pre-treatment neurological deficits, and are not deemed to be good operative candidates for a number of reasons.[2,18,28] Patient population biases make it difficult to compare different treatment modalities simply on the basis of a standard endpoint. As is true for so much of neurosurgery, a randomized study of surgical interventions for the treatment of trigeminal neuralgia would be helpful.

Along similar lines, it is even difficult to compare radiosurgical outcomes from multiple centers. Clearly, Gamma surgery for trigeminal neuralgia is one of the more straightforward types of radiosurgical cases. Most patients are treated with one isocenter, and the doses utilized from center to center vary very little. Nevertheless, there is a wide range in pain free and pain relief outcomes. Some of the differences between outcomes between radiosurgical centers may be a result of difference in patient populations. For instance, some centers may see more first time trigeminal neuralgia patients who have not had previous surgical interventions. However, the other causes for the difference in reported outcomes presumably are the fashion in which data was gathered (e.g. neurosurgical evaluation, follow-up mailed questionnaire or phone survey, referring physician interview, etc.), length of follow-up, and the rigorous criteria utilized to meet either “pain relief” or “pain free” status. Our results of 44% pain free outcome (without medication) at last follow-up and 70% with some degree of pain relief at 3 years follow-up are within the range reported by other centers (Table 4). These results are in close agreement with those reported by Brisman et al. (2002).[5] In that series of 179 patients, Brisman et al. (2002) reported an excellent outcome (no pain and not on any medicines) in 41% of patients.[5]

We believe it is better to grade patient outcome in intuitive and straightforward fashion by reporting pain free outcomes off medications. Such an endpoint is readily understandable to patients, neurosurgeons, and referring physicians of all backgrounds. Reporting outcomes in terms of subjective degrees of pain relief may lead to confusion for patients and physicians alike.

The variable history of trigeminal neuralgia is the other major difficulty in analyzing results from small to medium size retrospective studies. Trigeminal neuralgia can be characterized by spontaneous partial or complete remissions. The characteristic waxing and waning nature as well as the subjectivity of pain, sensory loss, and paresthesias makes a longer follow-up period and straightforward endpoints essential.

Prognostic Factors for Pain Relief

In our study, a univariate analysis revealed that a right sided pain distribution and a previous neurectomy were related to a pain free outcome. Multivariate analysis revealed that right sided pain and age correlated with a pain free outcome. In our study, it is notable that a pain free outcome was not related to dose, sensory loss, slight differences in target selection, or the type of pain (i.e. either atypical or typical trigeminal neuralgia). Although it is difficult to explain the observation that sidedness of trigeminal pain should effect outcome, this same relationship was observed in one large series of patients undergoing microvascular decompression.[36] The relationship between a previous neurectomy and Gamma surgery in terms of a pain free outcome suggests the efficacy of the Gamma Knife may not be reduced after a peripheral neurectomy. Clearly, the Gamma Knife and a peripheral neurectomy target proximal and distal portions of the symptomatic trigeminal nerve, respectively. In a subset of patients, it is possible that both proximal and distal portions of the nerve should be lesioned to provide adequate pain relief. The effect of age on outcome may in part be due to the generally older age of the patient treated with Gamma Knife (median age of 68) and the fact that many of these patients had had Gamma surgery as a first line treatment.

Other studies have reported different factors that were associated with a better response to Gamma Knife surgery. These include typical trigeminal neuralgia rather than atypical pain from multiple sclerosis or other causes[5,6], higher doses of radiation[27], a target closer to the brainstem[6], and no prior surgery[6,20]. Another favorable prognostic factor in patients with no prior surgical intervention is MRI evidence of blood vessel contact with the trigeminal nerve.[5] In the present study, we did not find these factors related to a pain free outcome.

Complications of Gamma Knife surgery

The most frequent complication following radiosurgical treatment of trigeminal neuralgia is facial numbness. The incidence of new trigeminal dysfunction varies from 6% to 66%.[19,20,24,26,27] Pollock et al. (2001) reported an association between higher radiation doses and the risk of trigeminal nerve dysfunction.[27] In that study, 54% of patients treated with 90 Gy experienced facial numbness whereas only 15% of patients treated with 70 Gy experienced a similar problem. In our series, 12 out of 136 patients (9%) developed new facial numbness following Gamma Knife surgery. In our study, only 1 patient received a dose of 90 Gy and no facial numbness was noted in this case. Fortunately, we did not observe cases of anesthesia dolorosa or absence of the corneal reflex in the 136 patients.

In our study, 29% of patients who had repeat Gamma surgery had new facial numbness whereas 7% of patients who had only one Gamma surgery developed new facial numbness (p=0.002, t-test). In a series of 18 patients who underwent repeat radiosurgery, Herman et al. (2004) noted an 11% incidence of new or worsened facial numbness which was not substantially elevated over the risk of facial numbness for those having only one Gamma surgery.[15] However, Hasegawa et al. (2002) and Shetter et al. (2002) noted an increased risk of facial numbness associated with repeat Gamma surgery.[12,32] It seems intuitively pleasing that the risk of facial numbness following repeat surgery even with dose reduction would be higher than for one surgery alone. However, the true incidence following Gamma surgery is not yet known and will require more extensive studies.

Conclusions

Gamma Knife surgery is a relatively safe and effective treatment option for patients with medically refractory trigeminal neuralgia. The minimally invasive nature of Gamma surgery makes this approach attractive for those patients with significant co-morbidities or an aversion to the more invasive yet more efficacious approach of microvascular decompression. The improvements in pain following Gamma surgery diminish somewhat with time, but this is true for other treatments as well. The time interval between treatment and pain improvement as well as the durability of the result remain the major limiting factors for Gamma Knife of trigeminal neuralgia.

Reference

1. Adrian ED: Proc Roy Soc B., 106:596, 1930.
2. Barker FG 2nd, Jannetta PJ, Bissonette DJ, et al: The long-term outcome of microvascular decompression for trigeminal neuralgia. **N Engl J Med 334:**1077-1083, 1996.
3. Brisman R: Gamma knife radiosurgery for primary management for trigeminal neuralgia. **J Neurosurg 93 Suppl 3:**159-61, 2000.

4. Brisman R: Gamma knife surgery with a dose of 75 to 76.8 Gray for trigeminal neuralgia. **J Neurosurg 100(5):**848-54, 2004.

5. Brisman R, Khandji AG, Mooij RB: Trigeminal Nerve-Blood Vessel Relationship as Revealed by High-resolution Magnetic Resonance Imaging and Its Effect on Pain Relief after Gamma Knife Radiosurgery for Trigeminal Neuralgia. **Neurosurgery 50(6):**1261-6, 2002.

6. Brisman R, Mooij R: Gamma knife radiosurgery for trigeminal neuralgia: dose-volume histograms of the brainstem and trigeminal nerve. **J Neurosurg 93 Suppl 3:**155-8, 2000.

7. Brown JA, Gouda JJ: Percutaneous balloon compression of the trigeminal nerve. **Neurosurg Clin N Am 8(1):**53-62, 1997.

8. Brown JA, McDaniel MD, Weaver MT: Percutaneous trigeminal nerve compression for treatment of trigeminal neuralgia: results in 50 patients. **Neurosurgery 32(4):**570-3, 1993.

9. Burchiel KJ, Clarke H, Haglund M, et al.: Long-term efficacy of microvascular decompression in trigeminal neuralgia. **J Neurosurg 69:**35-38, 1988.

10. Burchiel KJ, Slavin KV: On the natural history of trigeminal neuralgia. **Neurosurgery 46:**152-154, 2000.

11. Granit R, Leksell L, Skoglund CR: Fibre interaction in injured or compressed region of nerve. **Brain 67:**125-140, 1944.

12. Hasegawa T, Kondziolka D, Spiro R, et al.: Repeat radiosurgery for refractory trigeminal neuralgia. **Neurosurgery 50(3):**494-500, 2002.

13. Heidenhain R: Studien des Physiol Inst Zu Breslau. Leipzig, Germany, pp. 1-66, 1861.

14. Helfant MH, Leksell L, Strang RR: Experiences with Intractable Pain Treated by Stereotaxic Mesencephalotomy. **Acta Chir Scand 129:**573-580, 1965.

15. Herman JM, Petit JH, Amin P, et al.: Repeat gamma knife radiosurgery for refractory or recurrent trigeminal neuralgia: treatment outcomes and quality-of-life assessment. **Int J Radiat Oncol Biol Phys 59(1):**112-6, 2004.

16. Jannetta PJ: Aterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. **J Neurosurg 26:**Suppl:159-162, 1967.

17. Kondziolka D, Flickinger JC, Lunsford LD, et al.: Trigeminal neuralgia radiosurgery: the University of Pittsburgh experience. **Stereotact Funct Neurosurg 66 Suppl 1:**343-8, 1996.

18. Kondziolka D, Lunsford LD, Flickinger JC: Stereotactic radiosurgery for the treatment of trigeminal neuralgia. **Clinical Journal of Pain 18(1):** 42-47, 2002.

19. Kondziolka D, Lunsford LD, Flickinger JC, et al.: Stereotactic radiosurgery for trigeminal neuralgia: a multiinstitutional study using the gamma unit. **J Neurosurg 84(6):**940-5, 1996.

20. Kondziolka D, Perez B, Flickinger JC, et al.: Gamma knife radiosurgery for Trigeminal Neuralgia. **Arch Neurol 55:**1524-29, 1998.

21. Leksell L: Stereotaxic radiosurgery in trigeminal neuralgia. **Acta Chir Scand. 137(4):**311-4, 1971.

22. Leksell L: "Brain Fragments" translated by Melita Steiner in Radiosurgery: Baseline and Trends, Steiner L, Lindquist C, Forster D, Backlund E-O (eds), Raven Press, New York, 1992, pp. 263-292.

23. Lovely TJ, Jannetta PJ: Microvascular decompression for trigeminal neuralgia. Surgical technique and long-term results. **Neurosurg Clin N Am 8(1):**11-29, 1997.

24. Maesawa S, Salame C, Flickinger JC, et al.: Clinical outcomes after stereotactic radiosurgery for idiopathic trigeminal neuralgia. **J Neurosurg 94(1):**14-20, 2001.

25. Olivecrona H: Die Trigeminusneuralgie und ihre Behandlung. **Nervenarzt 14:**49-57, 1941.

26. Pollock BE, Foote RL, Stafford SL, et al.: Results of repeated gamma knife radiosurgery for medically unresponsive trigeminal neuralgia. **J Neurosurg 93 Suppl 3:**162-4, 2000.

27. Pollock BE, Phuong LK, Foote RL, et al.: High-dose trigeminal neuralgia radiosurgery associated with increased risk of trigeminal nerve dysfunction. **Neurosurgery 49(1):**58-62, 2001.

28. Pollock BE, Phuong LK, Gorman DA, et al.: Stereotactic radiosurgery for idiopathic trigeminal neuralgia. **J Neurosurg 97(2):**347-53, 2002.

29. Rand RW, Jacques DB, Melbye RW, et al.: Leksell Gamma Knife treatment of tic douloureux. **Stereotact Funct Neurosurg 61 Suppl 1:**93-102, 1993.

30. Regis J, Bartolomei F, Metellus P, et al.: Radiosurgery for trigeminal neuralgia and epilepsy. **Neurosurg Clin N Am 10(2):**359-77, 1999.

31. Rogers CL, Shetter AG, Fiedler JA, et al.: Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of the Barrow neurological institute. **Int. J. Radiation Oncology Biol. Phys. 47(4):**1013-1019, 2000.

32. Shetter AG, Rogers CL, Ponce F, et al.: Gamma knife radiosurgery for recurrent trigeminal neuralgia. **J Neurosurg 97(5 Suppl):**536-8, 2002.

33. Skoglund CR: The Response To Linearly Increasing Currents in Mammalian Motor and Sensory Nerves. **Acta physiol Scand Suppl 4(12):**7-75, 1942.

34. Steiner L, Forster D, Leskell L, et al.: Gammathalamotomy in Intractable Pain. **Acta Neurochirurgica 52:**173-184, 1980.

35. Taha JM, Tew JM Jr, Buncher CR: A prospective 15-year follow up of 154 consecutive patients with trigeminal neuralgia treated by percutaneous stereotactic radiofrequency thermal rhizotomy. **J Neurosurg 83(6):**989-93, 1995.

36. Wilson CB, York C, Prioleau G: Microsurgical Vascular Decompression for Trigeminal Neuralgia and Hemifacial Spasm. **West J Med 132:**481-481, 1980.

37. Young RF, Vermeulen SS, Grimm P, et al.: Gamma Knife radiosurgery for treatment of trigeminal neuralgia: idiopathic and tumor related. Neurology 48(3):608-14, 1997.

38. Young RF, Vermeulen S, Posewitz A: Gamma knife radiosurgery for the treatment of trigeminal neuralgia. **Stereotactic Functional Neurosurgery 70(suppl 1):**192-199, 1998.