

# The clinical efficacy and safety of stereotactic radiosurgery (gamma knife) in the treatment of trigeminal neuralgia

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Dr. Jennifer N.W. Lim led and undertook the review of the clinical efficacy and safety and also undertook the review of background information.

Professor Brian Ferguson, Nuffield Institute for Health, University of Leeds supervised and proof-read the review report.

Ms. Lynda Ayiku undertook the literature searches and obtained the papers.

All responsibility for the content of this review remains with the authors.

## **Lists of abbreviations and tables**

### **List of Abbreviations**

GKS	gamma knife radiosurgery
PGR	percutaneous glycerol rhizolysis
PRFR	percutaneous radiofrequency thermocoagulation rhizotomy
PBC	percutaneous balloon compression
MS	multiple sclerosis
TN	trigeminal neuralgia
MVD	microvascular decompression
Gy	Gray - unit of radiation dose in gamma knife radiosurgery
DREZ	Dorsal root entry zone

### **List of Abbreviations**

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**Figure 1**

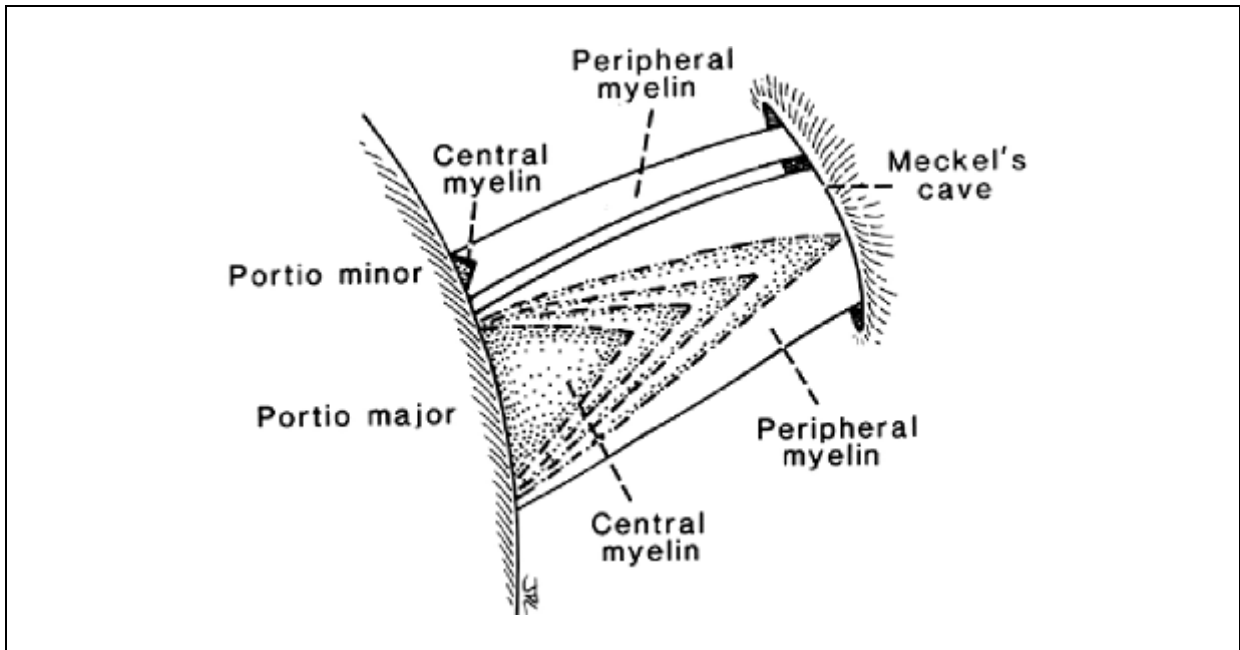
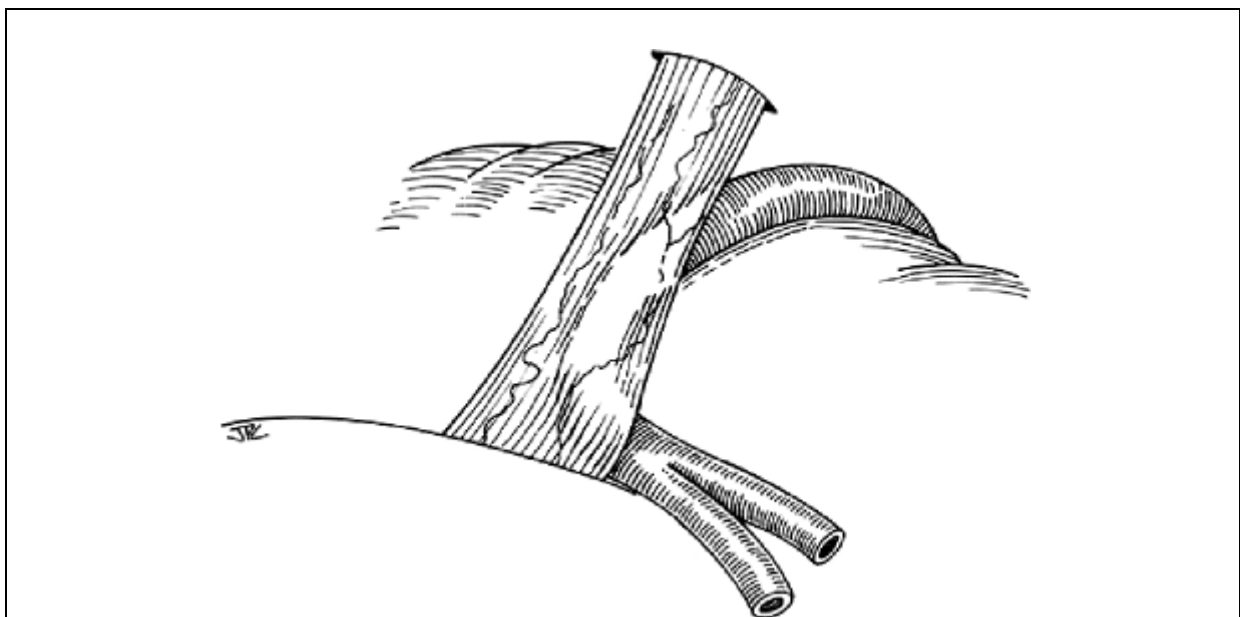


Diagram showing that the dorsal root entry zone of the trigeminal nerve can be variable in length and may extend to a more distal portion of the nerve.



Drawing of the most common vessel found causing typical trigeminal neuralgia, a rostroventral superior cerebellar artery loop, which compresses the trigeminal nerve either at the brainstem or distally.

*Illustrations and attached comments courtesy of the Journal of Neurosurgery: J Neurosurg 90:90, 1-8, 1999.*

# Executive summary

## Background

This review examines the clinical efficacy and safety of stereotactic radiosurgery (gamma knife) for the treatment of trigeminal neuralgia in patients with typical trigeminal neuralgia, multiple sclerosis patients and patients suffering from atypical trigeminal neuralgia.

Trigeminal neuralgia (TN) typically is described as a fleeting, stabbing pain occurring in the sensory distribution of the trigeminal nerve. The pain characteristically lasts seconds to minutes and the syndrome presents as episodes of shooting pain, electrical in nature. It was reported many centuries ago and is one of the few pain syndromes to have been relatively well investigated. The exact source of trigeminal neuralgia remains unknown, but it is generally accepted that focal demyelination in the root of the trigeminal nerve is involved in its pathogenesis which results in abnormal transmission and processing of impulses of the trigeminal nerve. TN is the most frequently occurring of the cephalic neuralgias in the population over 50 years of age. It is slightly more common in women (5.9 women per 100,000 population compared to 3.4 men per 100,000 population) with an age-sex adjusted incidence of 4.7 per 100,000 population. If left untreated and over time, the classical or typical syndrome of trigeminal neuralgia evolves and transforms gradually into a constant dull pain and the development of sensory disturbances. This new feature of trigeminal neuralgia is known as atypical trigeminal neuralgia. There are also TNs associated with multiple sclerosis (MS) and the average occurrence of trigeminal neuralgia in MS patients is 1% to 2%. First line treatment of the condition is by drug therapy and anti-convulsants can control symptoms in approximately 70% of patients. However, the majority of patients will eventually fail medical treatment and surgical procedures will then be considered.

Both major and minor surgical procedures are used to treat trigeminal neuralgia. The latest of the minor surgical procedures is stereotactic radiosurgery using the gamma knife. Other minor surgical procedures are: the three commonly performed percutaneous methods (radiofrequency thermocoagulation, glycerol rhizolysis and balloon compression) and the less widely used methods of local avulsion (removal) and cryotherapy of the peripheral branches of the nerve. There is only one type of major surgery, namely microvascular decompression, and that involves a craniectomy. In some cases, particularly when the exploration for microvascular decompression fails to find a vessel, partial rhizotomy (i.e. a partial division) of the nerve is performed. So far, no randomised controlled trials have been conducted on any of these surgical procedures. The evidence available is documented as case series studies.

## Objective

This review examines the clinical efficacy and safety of stereotactic radiosurgery using gamma knife in the treatment of typical trigeminal neuralgia, multiple-sclerosis trigeminal neuralgia and atypical trigeminal neuralgia.

## Methods

A literature search was carried out to identify all evidence relating to the use of gamma knife radiosurgery, microvascular decompression, and three percutaneous techniques (radiofrequency thermocoagulation rhizotomy, glycerol rhizolysis and percutaneous balloon compression) in the treatment of trigeminal neuralgia. The data sources used were 12

electronic bibliographic databases; the reference lists of relevant articles; related internet resources and practising gamma knife neurosurgery centres in the UK.

Studies were selected according to strict inclusion and exclusion criteria, and relevant information concerning clinical efficacy and safety was extracted directly onto an extraction/evidence table. The quality of the studies was assessed .

## **Results**

### **Number and quality of studies and direction of evidence**

In total, 23 case series studies were identified for gamma knife radiosurgery. Twenty-two are published case series studies with follow-up periods extending to just over two years (1 month to 26 months). The twenty-third is an unpublished case series study. This has an average follow-up period of eleven months (standard deviation five months), with data originating from the National Centre for Stereotactic Radiosurgery (Sheffield) in the UK. All the studies examined clinical efficacy by pain outcomes and pain recurrence rate, and safety by types of complications. Only one literature review was identified which compared all the four surgical methods. Differences between the studies and limitations in comparative data between the surgical techniques, however, make it difficult to draw any firm conclusions from this evidence.

### **Summary of efficacy and safety**

Trigeminal neuralgia patients benefited from gamma knife radiosurgery in terms of initial pain relief, a reported zero rate of operative mortality, a low rate of major complication risk, and only minor complications (paraesthesias). As a minimally invasive therapy with very low reported rates of operative mortality and major morbidity it is considered suitable for older patients (who may have concurrent medical illnesses or co-morbidity) and those patients who choose not to have major intracranial surgery<sup>7, 14, 15, 17, 25, 27</sup>. Reported pain recurrence rates vary from a high of 34% to a low of 0%, with an average of 14.4%<sup>6,7,9-21,24-26</sup> at follow-up periods that ranged from 1 month to 26 months.

## **Conclusions**

### **Generalisability of findings**

The review revealed a paucity of directly comparable data, a finding which has implications for the conclusions that can be drawn. Indirect comparisons have been shown to provide reliable results but the differences in case mix here do detract from the reliability of the data. A cautious interpretation however suggests that in typical trigeminal neuralgia, on the available evidence, gamma knife radiosurgery offers similar clinical efficacy, in terms of pain relief initially and on a short-term basis, as microvascular decompression, percutaneous radiofrequency thermocoagulation rhizotomy, percutaneous glycerol rhizolysis and percutaneous balloon compression. With regard to the safety of gamma knife surgery the available evidence suggests that it has a low complication risk compared to the other surgical techniques. Gamma knife surgery has a reported zero rate of operative mortality and a reported zero rate of disabling neurologic morbidity such as stroke when compared to other surgical techniques, particularly microvascular decompression.

However, the evidence mainly applied to those patients suffering from typical trigeminal neuralgia and the limited data does not allow a meaningful comparison to be made for other groups of trigeminal neuralgia patients. Therefore, the findings are not generalisable to multiple sclerosis and atypical trigeminal neuralgia patients.

### **Need for further research**

There is a need both for more long term data and randomised controlled trials which can take into consideration all the issues concerning radiation doses, radiation target area/zone, patient clinical characteristics, size of patient population, definition of pain outcomes, gamma knife model unit and length of follow-up period. Another aspect requiring further research is patient choice. Available evidence suggests that the choice of surgical procedure is determined by the availability of the gamma knife machine and the level of expert skill.

# Chapter 1 Background

## Description of the underlying health problem

### Definition of the condition - trigeminal neuralgia

Neuralgia is a clinical term used to define a pain that usually occurs in intermittent, recurrent paroxysms and radiates throughout or within an area of specific nerve distribution<sup>1</sup>. Trigeminal neuralgia (TN) typically is described as a fleeting, stabbing pain occurring in the sensory distribution of the trigeminal nerve. The pain characteristically lasts seconds to minutes and the syndrome presents as classic episodes of shooting pain, electrical in nature.

The condition or attacks are usually triggered by stimuli such as talking, eating, cleaning the teeth, or even a cool temperature or wind on the face. Light tactile stimulation is often all that is needed to provoke a volley of paroxysms, and this can be so profound that sufferers will neglect grooming on the affected side of the face. Washing the face, brushing the teeth and eating on the affected side may be avoided; the sufferer may even pool his/her saliva for fear of swallowing.

Traditionally trigeminal neuralgia was known as tic douloureux or idiopathic neuralgia because of its unknown causes. There are two types of TN, namely primary and secondary. Primary TN is a genuine TN that occurs in the absence of visible organic lesions while secondary TN is a complication of such lesions. Primary TN is also referred to as typical TN, or essential TN, and sometimes is loosely referred to as idiopathic TN. Primary TN occurs when the trigeminal nerve is compressed by a vascular loop (which may not always be visible) at the sensory root entry zone of the nerve which can subsequently result in damage to the nerve's myelin sheath. Facial pain can occur in three parts of the face, namely ophthalmic (V<sub>1</sub>), maxillary (V<sub>2</sub>), and mandibular (V<sub>3</sub>) for the three divisions of the trigeminal nerve in the face. The division of the trigeminal nerve most commonly affected is V<sub>2</sub> (35%), followed by V<sub>3</sub> (29%) and V<sub>1</sub> (4%) being the least common. The maxillary (V<sub>2</sub>) and mandibular distribution (V<sub>3</sub>) are simultaneously affected in 19% of cases and all three divisions together in 1%<sup>2</sup>. Sufferers are mainly older people, people with multiple sclerosis, and people with certain types of meningioma tumour but for the majority of patients there is no obvious cause (other than a vascular loop).

The clinical association of TN with MS is established in three large series<sup>36,37,38</sup>. These studies revealed an average TN incidence of 1% to 2% in MS patients. TN usually begins 10 years after the first symptoms of MS, but in some patients TN may be the first or only symptom of MS. Facial pain in MS is usually indistinguishable from that of classical TN but a substantial number of cases may fall into the atypical category. Bilateral TN is significantly more common in MS patients<sup>36</sup>. A 5% incidence of bilateral TN was found<sup>39</sup> in the non-MS population compared to 18% in MS patients.

Atypical TN is primary TN which is left untreated over time and has new pain features such as constant dull pain and sensory impairment.

### Classic clinical criteria of trigeminal neuralgia

The classic description of TN details several clinical criteria:

1. Pain is localised to one or more branches or divisions of the trigeminal nerve;
2. Pain is sharp, shooting, stabbing, 'electric shock'-like and occurs as a brief episode or attack, lasting several seconds with pain-free intervals between attacks;
3. Attacks are initiated by stimulation of so-called 'trigger zones' or they may start without obvious provocation;
4. The disease usually involves remissions of pain, which may last years and even decades;
5. Pain syndrome almost uniformly responds to oral carbamazepine;
6. The diagnosis of TN also assumes preservation of the function of the trigeminal nerve, with only mild hypaesthesia in some cases

### **Pathogenesis of primary trigeminal neuralgia**

The exact nature of the pain or TN source remains unknown, but it is generally accepted that focal demyelination in the root of the trigeminal nerve is involved in its pathogenesis. This demyelination results in the abnormal transmission and processing of impulses of the trigeminal nerve. As mentioned earlier this demyelination can be due to compression from a vascular loop<sup>4</sup>. Additional types of neurovascular relationships have also been observed<sup>5,87</sup>: an artery distorting the root of the trigeminal nerve or wedged between the nerve root and the pons; an artery just in contact with the root; the artery to root relation merely being venous contact or a distortion, or 'no abnormality'<sup>5,87</sup>. Demyelination could also be a result of multiple sclerosis and there is autopsy evidence of demyelinating plaques in the dorsal nerve root entry zone, descending trigeminal tracts, or brainstem nuclei in patients with concurrent trigeminal neuralgia<sup>41,49</sup>.

For atypical TN, a theory of progressive change involving sequential stages of the same disease process has been proposed by Burchiel and Slavin<sup>3</sup>. Atypical TN is a result of TN that has been left untreated. Over time there is a gradual transformation which involves change in the character of pain from the classic episodes of shooting pain of TN to constant pain and development of sensory impairment.

### **Epidemiology**

#### ***Mortality***

Deaths that result directly from trigeminal neuralgia are rare. When fatalities do occur they are almost always the result of a surgical intervention. Microvascular decompression carries a mortality rate as high as 14%<sup>2</sup>.

#### ***Incidence and prevalence***

TN is the most frequently occurring of the cephalic neuralgias in the population over 50 years of age. It is slightly more common in women (5.9 females compared to 3.4 males per 100,000 population) with an age-sex adjusted incidence of 4.7 per 100,000 population<sup>2</sup>. It is experienced more often on the right side of the face than on the left (unilateral) and occurs on both sides of the face (bilateral) at one time or another in 4% of TN patients. Multiple sclerosis is the most common predisposing factor for bilateral TN<sup>1</sup>.

### **Significance in terms of ill health**

The disorder is frequently associated with a gradual worsening of the pain pattern characterised by increased pain severity and a shortening of the pain-free intervals. If left untreated it may develop new features, including sensory disturbances and constant pain,

which are uncharacteristic of TN, and evolve toward another pain syndrome generally known as atypical TN<sup>3</sup>.

The goal of treatment is to achieve optimal control of the disease by eliminating the pain or at least reducing the pain to a level acceptable by sufferers.

## **Current service provision**

TN is currently treated by a variety of pharmacological agents and surgical interventions usually provided by specialist neurology services.

## **Medical Management**

First line treatment is drug therapy and anti-convulsants can control symptoms in many patients. Approximately 70% of TN patients are well-controlled non-operatively.

Carbamazepine therapy is the most effective anti-convulsant and is the first line drug for treatment of TN. Approximately 75% of patients respond to carbamazepine<sup>123</sup> and this is used by some doctors as a diagnostic criterion. However, the use of carbamazepine is limited by the development of hypersensitivity reactions or side-effects such as drowsiness, decreased mental acuity, subjective dizziness and ataxia in older patients, dose-related mild leucopaenia, or a very rare non-dose dependent idiosyncratic bone marrow suppression which can occur early in the course of the treatment. Other drugs used are gabapentin, baclofen and phenytoin.

Although most patients are well-controlled by drugs initially, many will become non-responsive and breakthrough of pain begins. Control of the symptoms of the majority of patients will eventually fail on medical treatment and surgical procedures will be considered.

## **Surgical treatments**

When patients' symptoms are intractable to medical management, surgical treatments are considered depending on patient-disease characteristics, equipment availability, expert skills availability, and patient choice. The latest technological development is stereotactic radiosurgery using gamma rays sometimes called 'gamma knife radiosurgery' (GKS). There are three other procedures considered to be minor surgery, namely, percutaneous retrogasserian glycerol rhizolysis (PGR), percutaneous radiofrequency trigeminal gangliolysis or radiofrequency thermocoagulation rhizotomy (PRFR), and percutaneous trigeminal ganglion compression or balloon compression (PBC), all of which also offer minimal anaesthetic risk and morbidity/mortality, and utilize local or brief general anaesthetics without endotracheal intubation. Patients who undergo these procedures are usually discharged on the same day of treatment. As minimally invasive procedures stereotactic radiosurgery and percutaneous techniques are particularly suited for the elderly or ill patients who do not desire or are poor candidates for a major operative procedure such as microvascular decompression (MVD)<sup>7, 14, 15, 17, 25, 27</sup>. These procedures are described in more detail below.

### ***Percutaneous retrogasserian glycerol rhizolysis***

Glycerol is injected into the cistern of Meckel's cave under fluoroscopic guidance<sup>2</sup>.

### ***Percutaneous radiofrequency trigeminal gangliolysis or radiofrequency thermocoagulation rhizotomy***

PRF is carried out using a hollow 19-gauge needle, insulated except for the tip. The needle is advanced into the foramen ovale under fluoroscopic guidance in a similar manner to glycerol rhizolysis<sup>2</sup>.

### ***Percutaneous trigeminal ganglion compression***

PBC is performed with the patient under general anaesthesia. A No.14 needle is inserted under fluoroscopic guidance into the foramen ovale. Then a No.4 French Fogarty embolectomy catheter is advanced 15 to 20 mm into the needle and inflated with non-ionic water solution radiocontrast solution to achieve a pear shape in Meckel's cave<sup>2</sup>.

### ***Microvascular decompression***

MVD is the most radical technique, involving open-skull surgery either to 're-arrange' the vascular loop to protect the nerve from pressure or to remove a lesion. It is a major surgical procedure requiring a thorough preoperative evaluation of cardiopulmonary, haematologic, and coagulation status<sup>2</sup>. It involves general endotracheal anaesthesia so that craniectomy can be carried out.

Since treatment by GKS is dependent on access to a gamma knife radiosurgery centre/gamma knife unit, the choice of treatment technique is restricted to percutaneous and MVD techniques in most centres. Which of the latter approaches is chosen is dependent on the age of the patient, the anatomical involvement of the trigeminal nerve and patient preference. Assuming the unavailability of GKS, Das and Saha<sup>125</sup> recommended the following options:

- (1) If the patient is over 70 years old, in poor health and the TN is restricted to a single division of the trigeminal nerve, then peripheral neurolysis or peripheral neurectomy are the modalities of choice.
- (2) If the patient is old, incapacitated and the pain involves multiple divisions, then PBC or PRFR or PGR are the options.
- (3) If the patient is young, in good health and medical therapy is ineffective, MVD is the treatment of choice. Partial section of the nerve is recommended if definite vascular compression is not identified.
- (4) If the patient is young but chooses not to have any operative intervention, percutaneous techniques are the alternative options.
- (5) MS-TN (and atypical TN) patients of any age may choose any of these options.
- (6) In cases of recurrence after MVD, the best approach is by percutaneous techniques or by division of the sensory root at the pons. The patient should be treated as a new case if pain recurs after percutaneous treatment.

### ***Gamma knife radiosurgery - the interventional procedure***

The gamma knife is a complex machine that uses cobalt 60 as its energy source, and is able to focus a precise intersection of beams of gamma rays to perform radiosurgery. The target is clearly defined through the use of high-resolution CT and MRI scans coupled with computer technology. GKS is a minimally invasive technique and, when used in the treatment of TN, the trigeminal nerve is targeted at the location of an imaged vascular compression, or at the site of exit of the trigeminal nerve from the pons or at a particular position on the trigeminal nerve if no compressing vessels are identified. Target doses reported are between 35 to 100 Gray units (Gy) with an average between 70 to 90 Gy.

Currently there are three gamma knife machines in the United Kingdom. There is an NHS-funded machine in the National Centre for Stereotactic Radiosurgery, Sheffield Teaching Hospitals NHS Trust, which was installed in 1985 and replaced with Model C in 2001. Gamma knife surgery is also being carried out in the London Radiosurgery Centre, St Bartholomew's and the London NHS Trust and the Gamma Knife Centre, Cromwell Hospital, London.

Gamma knife radiosurgery starts with the fitting of a head frame that is secured to the head by 4 metal screws and stays in place throughout the treatment. A local anaesthetic is given. The patient then has a CT or MRI scan and based on this, the neurosurgeon then 'plans' the treatment. At this point the patient lies down on a couch and a 'treatment helmet' is positioned over the head frame. The couch is then wheeled into the gamma knife machine and treatment commences.

Gamma knife radiosurgery is a relatively new surgical treatment for primary trigeminal neuralgia, with the earliest study published in 1996<sup>14</sup>. Many case series studies in this review were assessing the optimal radiation dosage<sup>6-8,11,13,14,17</sup>, target area/zone<sup>14,19,22,25,26</sup> or whether it should be used as the primary surgical treatment<sup>9,10,12,18,22</sup>, the clinical efficacy and safety as a repeat treatment<sup>24</sup> and how different patient groups responded to this treatment<sup>18,21</sup>.

## **Guidelines on trigeminal neuralgia management**

The current National Institute for Clinical Excellence (NICE) provisional guidance on gamma knife radiosurgery for trigeminal neuralgia recommends its use only under special arrangements for consent and for audit or research, due to inadequate evidence on its efficacy and safety<sup>35</sup>. Clinicians wishing to perform this procedure are advised to inform their clinical governance leads, to ensure that patients are informed of the uncertainty involving its efficacy and safety and are provided with clear written information, and to ensure that appropriate arrangements are in place for audit and research.

## **Scope of the review**

The aim of this review is to appraise "the efficacy and safety of the use of gamma knife radiosurgery in the treatment of primary trigeminal neuralgia, multiple-sclerosis related TN and atypical neuralgia".

To address this question, comparison has been made between gamma knife radiosurgery as the interventional procedure and four other surgical procedures, namely, microvascular decompression and all the three percutaneous techniques described above.

## Chapter 2 Safety and Efficacy

### Methods for reviewing safety and efficacy

#### Search strategy

The search aimed to identify all articles relating to the safety and efficacy of stereotactic radiosurgery (gamma knife) in the treatment of trigeminal neuralgia. In relation to the comparative alternative treatment techniques the searches also aimed to identify all articles previously addressed in the literature review by Moore and Burchiel<sup>2</sup> and published subsequent to that literature review. Moore and Burchiel's review is being used here in preference to that of Nugent (2000)<sup>32</sup> because it covers all the alternative treatment techniques including microvascular decompression which Nugent did not include. All literature searches were conducted between May and August 2003.

#### Sources searched

Twelve electronic bibliographic databases were searched, covering biomedical, health-related, science, social science, and grey literature. A list of databases is provided in Appendix 1. In addition, the reference lists of relevant articles and Moore and Burchiel<sup>2</sup> were checked.

#### Search terms

##### *Gamma Knife Radiosurgery - interventional procedure*

A combination of free-text and thesaurus terms were used. The disease terms (e.g. trigeminal neuralgia, trigeminal nerve disease, idiopathic neuralgia, facial pain, etc.) were combined with the 'Intervention' terms (e.g. gamma knife, radiotherapy, stereotactic radiosurgery, etc.) Copies of the search strategies used in the major databases are included in Appendix 1.

##### *Microvascular Decompression (MVD) and Percutaneous Techniques - (Comparatives)*

Further searches were performed to identify the more common treatments for trigeminal neuralgia so that a comparison with the safety and efficacy of gamma knife could be gained. The disease terms (e.g. trigeminal neuralgia, trigeminal nerve disease, idiopathic neuralgia, facial pain, etc.), were combined with the 'Comparative' terms (e.g. Microvascular decompression and three percutaneous techniques, namely, glycerol rhizolysis; balloon compression; and radiofrequency thermocoagulation). Copies of the search strategies used in the major databases are included in Appendix 1.

#### Search restrictions

No date or language restrictions were applied. Due to the small number of references retrieved from the databases methodological search filters for safety and efficacy were not deployed in the searches.

### Inclusion and exclusion criteria

#### *Applying to all articles*

##### *Inclusion criteria*

- Participants: All patients suffering from trigeminal neuralgia as a primary cause, patients suffering TN due to multiple sclerosis and patients suffering from atypical TN are included.

- Intervention: Use of gamma knife radiosurgery in the treatment of trigeminal neuralgia.
- Comparators: Four other techniques used to treat TN are compared. They are microvascular decompression, and the three percutaneous techniques (PRFR, PGR and PBC).

#### *Exclusion criteria*

- Participants: Patients with secondary TN i.e. due to growth of organic lesions or tumours are excluded from this study.
- Interventions: Other forms of stereotactic radiation treatment such as the Linear Accelerator are excluded from this study.
- Language: Any articles not available in the English language (this review was subject to a short timescale that precluded time for translation).
- Time: No date limits were imposed.
- Abstracts: Studies available only as abstracts were excluded.
- Case Reports: Studies available as individual case reports were also excluded.

#### ***Applying specifically to comparative techniques of treatment of trigeminal neuralgia***

Due to time constraints, articles on alternative techniques (MVD, PBC, PRFR and PGR) that had previously been selected based on the above criteria were reviewed a second time against the following criteria:

- Length of follow-up and number of patients: Studies with the longest follow-up period and largest patient size are included.
- Type of patients: Studies that covered a full range of TN patients including those with MS and atypical pain features.
- Year of publication: Due to time constraint, only the most recent studies that had not been identified by Moore and Burchiel<sup>2</sup> are included.

Using these criteria, three studies in addition to the ones reviewed by Moore and Burchiel were included in this review.

#### **Data extraction strategy**

All abstracts, and the titles of those articles for which abstracts were not available, were read by two reviewers and a consensus was reached on which articles should be acquired for further consideration of the evidence based upon the full text. All articles were read and appraised by the reviewer who extracted relevant information, transferring it directly to an extraction/evidence table.

#### **Quality assessment strategy**

Only non-randomised, case series studies were found in all the searches. The quality of the studies was assessed using a checklist based on the Centre for Reviews and Dissemination's Guidance<sup>33</sup> and Downs and Black<sup>34</sup>.

## Results

### Quantity and quality of research available

#### *Number of references*

A total of 611 references were identified from all the searches carried out, of which 217 references were for GKS and 394 for the MVD and three percutaneous techniques.

Based on the relevance of the abstracts 48 references were ordered on the GKS technique and 70 articles ordered for alternative methods. Twenty-two case series on GKS and four articles on the four alternative treatment techniques met the criteria for inclusion and were reviewed (Table 1). One of the four articles on alternative treatment techniques is a literature review by Moore and Burchiel (1996)<sup>2</sup>. This article is chosen over Nugent (2000)<sup>32</sup> because it covered all the alternative treatments while Nugent only discussed the 3 percutaneous techniques and did not review the evidence on microvascular decompression (MVD). The remaining three articles on alternative treatment are the most recent and have the largest patient size and longest follow-up period. Two studies specifically referring to multiple sclerosis patients and atypical trigeminal patients were also reviewed. Reasons for articles being excluded are given in Appendix 2.

#### *Research registers*

Searches of the National Research Registers on gamma knife radiosurgery did not yield any additional studies.

#### *Practising neurosurgical centres in the U.K.*

The neurosurgeons in the three hospitals in the UK who are treating TN with GKS were contacted for their data. The neurosurgeon from the private hospital did not reply to both telephone and email messages. The neurosurgeon from the London Radiosurgery Centre could not share his data as yet. The neurosurgeon from the National Centre for Stereotactic Radiosurgery, Sheffield provided his unpublished data<sup>138</sup> and this evidence is included in this review (Appendix 5).

**Table 1 : Number of references**

Topic	No.identified*	No.ordered/ contacted	No. meeting criteria	
			RCTs	Non-RCTs
Efficacy and safety				
- GKS				
Published studies	217	48	0	22
Unpublished study <sup>138</sup>	1	1	0	1
- Comparative techniques	394	70	0	6
Current research	0	0	0	0
Total	-	118	0	29

\* includes duplicates

RCT, randomised controlled trials

#### *Quality assessment of the evidence on gamma knife surgery*

The quality of the evidence was assessed using a checklist derived from the Centre for Review and Dissemination's Guidance<sup>33</sup> and Downs and Black<sup>34</sup>. A summary of the quality assessment of the 23 case series studies on gamma knife radiosurgery is provided in Table 2.

All the case series reviewed only included patients who had undergone gamma knife radiosurgery carried out by the authors. Twenty studies clearly described their inclusion and exclusion criteria while 3 did not. None of the studies stated whether patients entered the study at similar point in their disease progression. Even though some studies provided information such as pain duration<sup>6,9,17-20,25-27</sup> and history of prior surgery<sup>6,8,9,10-15,18-19,21,23,25-27</sup>, the exact point and severity of this disease condition is difficult to determine considering that the pathogenesis of this disease still remains unclear.

**Table 2 Summary of the quality assessment of the 23 case series studies on GKS**

Criteria	Yes	No	Unclear
1. Were participants a representative sample selected from a relevant patient population?	23	0	0
2. Are the inclusion/exclusion criteria of patients in the study clearly described?)	20	3	0
3. Were participants entering the study at a similar point in their disease progression?	0	0	23
4. Was selection of patients consecutive?	0	0	23
5. Were all important prognostic factors identified?	23	0	0
6. Was data collection undertaken prospectively?	1	0	22
7. Was the recruitment period clearly stated?	18	5	0
8. Was the intervention that which is being considered in the review? (or was it a significant modification?)	23	0	0
9. Was an attempt made to blind outcomes assessors?	8	14	1
10. Was the operation undertaken by someone experienced in performing the procedure?	23	0	0
11. Did the staff, place, and facilities where the patients were treated provide an appropriate environment for performing the procedure? (e.g. was the intervention undertaken in a centre with the necessary back-up facilities?)	23	0	0
12. Were objective (valid and reliable) outcome measures used?	22	1	0
13. Were all the important outcomes considered?	22	1	0
14. Was follow-up long enough to detect important effects on outcomes of interest?	1	22	0
15. Was information provided on non-respondents, dropouts?	8	2	13
16. Were participants lost to follow-up likely to introduce bias? (e.g. high drop-out rate; no description of those lost)	2	8	13
17. Were the main findings clearly described? (to allow replication)	23	0	0

In all the studies it is unclear whether patients were selected consecutively as no information is provided. From the information provided on the duration of follow-up, it would seem that patients entered the study after they had undergone GKS treatment. All studies identified important prognostic factors. Eighteen of the studies stated the recruitment period while the rest did not. All the studies examined the clinical efficacy and safety of the interventional procedure (GKS). In 7 studies<sup>6,7,10,17,18,24,25</sup>, attempts were made to single-blind the outcome assessors while the rest did not and it was unclear in one study. One study, assessing whether

the length of the nerve irradiated affected the outcome<sup>19</sup>, was a double-blinded study with patients blinded to the second isocentre being irradiated.

All the surgical procedures were conducted in an appropriate environment and performed by neurosurgeons. Only in one study<sup>26</sup> was the pain outcome defined broadly. All important outcomes were considered with regard to pain relief, pain recurrence, and complications. The issue of pain relief assessment and the extent to which it may be said to have been rigorously assessed by the different studies is discussed further in Chapter 3. Despite the variation in definitions used there are grounds for taking the view that the reported comparisons do represent a real difference in pain experience. None of the studies, except one<sup>138</sup>, however, have long follow-up periods. The average follow-up period for the 22 published case series studies was 17.8 months with the longest follow-up period being 24 months (mean)<sup>13</sup> while the shortest, was 1 months<sup>9</sup>. The unpublished case series study has a follow up period of 11 months plus or minus five months<sup>138</sup>.

Eight studies<sup>6,7,10,11,17,19,22,25</sup> provided information on non-respondents or dropouts but the number of patients lost to follow up in 5 studies<sup>6,7,17,22,25</sup> was considered likely to introduce bias. All the studies clearly described their main findings.

## **Clinical efficacy of GKS**

### **Review question**

The study question for this review was to appraise “the efficacy and safety of the use of gamma knife radiosurgery in the treatment of primary trigeminal neuralgia, multiple-sclerosis trigeminal neuralgia and atypical trigeminal neuralgia”.

In assessing the clinical efficacy of GKS, this review appraises two factors, i.e. levels of pain relief and pain recurrence. In order to compare the clinical efficacy and safety of the use of GKS with MVD, PBC, PGR and PRF, this review uses the literature review of Moore and Burchiel<sup>2</sup> for evidence/studies published before 1996 and the three most recent studies on these techniques. Safety is assessed by the types and rates of complications due to surgical treatment.

### **Pain outcomes/relief after gamma knife radiosurgery**

#### ***Evidence based on 22 published case series studies***

Contained in Appendix 3 is the data abstraction table of the 22 studies.

Tools for assessing pain are not well described. Where this information was given pain assessment methods involved the self-reporting of pain levels by patients with this data being obtained from telephone or mail questionnaires or from direct questioning by surgeons. Table 3 displays the pain outcomes reported initially after GKS treatment and at the last follow-up for the 22 published case series. At a mean follow-up of 17.8 months<sup>6,8-21,24-27</sup>, the data on initial pain response revealed that between 33% and 90% of patients achieved complete pain relief after GKS procedure, with an average of 58.3%. At the last follow-up in these 19 studies, between 35% and 80% of patients were completely pain free. Based on available data from eight studies<sup>6,9,13,15,18,19,22,24</sup>, the percentage of patients who achieved complete pain relief at the last follow-up compared to initially decreased in almost all the case series by 6.5% on average (0 - 13.6%). In one study, the number of patients achieving complete pain relief remained unchanged throughout the study period<sup>15</sup>.

On average, 71.1% of patients achieved more than 50% pain relief after GKS treatment at last follow-up<sup>8-19,21,25,27</sup>. The percentage of patients achieving more than 50% pain relief ranges from 45% to 96%.

### ***Evidence from an unpublished case series study (Appendix 5)***

This study<sup>138</sup> observed that 65.9% of patients (31/45) with typical TN achieved complete pain relief and 82.9% experienced at least more than 50% improvement after treatment with GKS.

### **Pain recurrence after gamma knife radiosurgery**

The pain recurrence rate from the published evidence was as low as 0% and as high as 34%, with an average of 14.4%<sup>6,7,9-21,24-26</sup> at follow up periods ranging from 6 months to 26 months. Two studies reported no pain recurrence<sup>15,16</sup> (Table 3). Based on the unpublished study<sup>138</sup>, only one recurrence was observed amongst 31 patients who achieved complete pain relief.

**Table 3 Summary of pain outcomes, pain recurrence after gamma knife surgery**

Authors	Patient size	Follow-up, months period of study	Radiation dosage, Gy	%, Initial complete pain relief, no medication	At last follow-up, complete pain relief, no medication, %	At last follow-up ≥ 50% pain relief <sup>a</sup> , %	Pain recurrence rate, %
Pollock et al, 2001 <sup>6</sup>	68	14.4 (median) 4/1997-12/1999	70 90	56 59	41 61	67 (at initial) 76 (at initial)	26 15
Regis et al, 1999 <sup>7</sup>	75	3 - 60	75 - 90	87	79	93 (at initial)	10
Nicol et al, 2000 <sup>8</sup>	42	14 (median) (3 - 30)	90	73.8 <sup>b</sup>	n/s	95	n/s
Pollock et al, 2002 <sup>9</sup>	117	26 (median)(range 1 – 48 mo) 4/1997 - 8/2000	70, 80, 90	59	55 (at year 3)	55 (at year 3)	22.7
Young et al, 1998 <sup>10</sup>	110	19.8 1/1990-1/1998	70, 80	76.4	n/s	88.2	34
Rogers et al, 2000 <sup>11</sup>	54	17	35, 40	35	n/s	83	20.7
Rogers et al, 2002 <sup>12</sup>	15 <sup>c</sup>	17	70,80,90	33	n/s	80	33
Maesawa et al., 2001 <sup>13</sup>	220	24 max = 6.5 years	60 - 90	47.7	40 at 6.5 years 75.4 at 33 mo	69.1 55.8 at 5 year for both complete and partial relief	13.6 (between 3 to 58 mo)
Kondziolka et al, 1996 <sup>14</sup>	50	18 (11 - 36)	60 - 90	n/s	56 58 at 2 year	36 at year 2	6
Kondziolka et al, 1997 <sup>15</sup>	80	18 (11 - 36)	60 - 90	46.3	46.3	76.3	0
Kondziolka et al, 1998a <sup>16</sup>	23 <sup>d</sup>	12 (5 - 33)	70, 80	-	74	96	0
Kondziolka et al, 1998b <sup>17</sup>	121	18 1993 - 1997	70 - 90	60	-	77	10
Kondziolka et al 2002 <sup>18</sup>	220	22	60 - 90	47.7	40	68.6	13.6
Flickinger et al, 2001 <sup>19</sup>	87	26 (1 - 36)	75	51.1	37.5	48.9	13.8
Zheng et al, 2001 <sup>20</sup>	80	23.7 (12 - 43) 11/1996- 4/1999	70 - 90	52.5	n/s	93.8 (initial response)	8.75
Urgosik et al,	49	13	70, 80	n/s	62 <sup>e</sup>	77	18.4

1998 <sup>21</sup>		10/1995 - 10/1996					
Brisman & Mooij, 2000 <sup>22</sup>	126	At 6 mo & 12 mo 5/1998 - 2/2000	75	41 at 6 mo	37 at 12 mo	n/s	n/s
Brisman, 2000 <sup>23</sup>	126	At 6 mo & 12 mo 5/1998-2/2000	75	77 at 6 mo	50 at 12 mo	n/s	n/s
Pollock et al, 2000 <sup>24</sup>	11	15 (3 - 32) 4/1997-12/1999	80	90	80 (at med 15mo)	n/s	11.1
Hasegawa et al, 2002 <sup>25</sup>	27	22.3 (6 - 73) 1997 - 2002	64.4	n/s	59.3 (1st GKS) 48.1 (2nd GKS)	85.2(1st GKS) 85.2(2ndGKS)	17.4
Kannan et al, 1998 <sup>26</sup>	7	10 1/1997-1/1998	70, 80	n/s	57 in May/1998	0	n/s
Han et al, 1999 <sup>27</sup>	43	9 (2 - 23)	70, 80	n/s	35	45	n/s
National Centre for Stereotactic Radiosurgery, 2003 <sup>138</sup>	64	11 months ± 5 months 1996 - 2001	80	n/s	65.9	82.9	3 <sup>f</sup>

<sup>a</sup> Figures include patients who achieved complete pain relief without the use of medication and those who achieved at least 50% pain relief and continued with use of medication.

<sup>b</sup> Including patients who still use medication for fear of pain return, on low dosage or for seizures.

<sup>c</sup> All patients are suffering from multiple sclerosis.

<sup>d</sup> None of the patients had any prior surgery before GKS treatment.

<sup>e</sup> Pain outcome/level includes patients with residual pain of 0-20%.

<sup>f</sup> Only amongst patients who achieved complete pain relief.

“n/s” = not stated.

## Comparison with MVD, PBC, PGR and PRFR

Table 4 summarises the literature review by Moore and Burchiel<sup>2</sup>, and Appendix 4 is the data abstraction table for the three recent and largest case series studies on alternative techniques to treat trigeminal neuralgia.

Two areas addressed by Moore and Burchiel<sup>2</sup> are of relevance to this review:

- the efficacy of these techniques in terms of pain relief and pain recurrence rate;
- any complications due to the use of these techniques.

In both areas, Moore and Burchiel<sup>2</sup> included studies that were identified and selected at the beginning of this review.

### Pain relief

Taking both published and unpublished evidence, the data from the 23 case series on GKS revealed that complete pain relief was achieved by 33% - 90% of patients immediately after GKS treatment and by last follow-up for 35% - 83% of patients. On average, 71.8% of patients achieved at least 50% pain relief after GKS treatment<sup>8-19,21,25,27,138</sup>. These figures are in accordance with those of the alternative techniques used to treat trigeminal neuralgia (Table 4).

The percentage of patients achieving good or effective pain relief after PGR treatment was 72% - 96% within 48 hours, 78% - 100% immediately after PRFR treatment, 78% - 100% immediately after PBC and 70% - 96% immediately after MVD treatment.

## Pain recurrence rate

Pain recurrence rate for GKS, based on published data only, was on average 14.4% (0% - 34%) over a follow-up period of on average 17.8 months (ranging from 9 to 26 months)<sup>6,8-21,24-27</sup>; compared to 27% for PGR at 12 months; 4% - 32% for PRFR at 12 months; 55% - 77% at 3 year for PBC; and for MVD, 2% per year and 17% - 26% at 5-year. Evidence from the Sheffield data<sup>138</sup> revealed 3% or 1 recurrence in 31 patients who were pain free from May 1996 to December 2001<sup>1</sup>.

**Table 4 Pain outcomes and recurrence rate after glycerol rhizolysis, radiofrequency thermocoagulation rhizotomy, balloon compression and microvascular decompression**

Reference, type of surgical procedure	Effective pain free (complete and good)	Technical failure <sup>1</sup>	Recurrence pain rate, % Time to recurrence (mo)
Glycerol rhizolysis (PGR) <sup>2</sup>	Effective relief achieved within 48 hrs for 72% - 96% of patients.	15%	At 1 yr = 27% (18.5 - 72% over follow-up of 3 to 72 mo)  Med. time to recurrence = 16 - 36mo.
Radiofrequency thermocoagulation rhizolysis (PRFR) <sup>2</sup>	Immediate = 78-100%	6 - 7%	At 1 yr = 4 - 32% At 3 yr = 10 - 66%  Average time to recurrence = 18.5 mo Re-operation rate at 5 yr = 21 - 28%
Ganglion compression /Balloon compression (PBC) <sup>2</sup>	Immediate = 89.9-100%	20% at 60 mo  30% at 12 mo.	At 3 yr = 55 - 77.4% At 11 yr = 30% Majority recurred within 48mo.  Average time to recurrence = 4.2 - 6.5 mo. 5-yr recurrence rate = 13%
Microvascular decompression (MVD) <sup>2</sup>	Immediate = 70-96% At 48mo = 72% excellent results, 83% satisfactory, At 100mo, 58% are pain free, 12% minor recurrences, 30% major recurrences	n/s	Per year = 2% (3.5% for major recurrences, 1.5% for minor recurrences per year)  5-yr recurrence rate = 17-26% Ave. time to recurrence = approx. 2 yrs at which time 12% have recurrences.
MVD <sup>31</sup>	92.1% (6mo after surgery)	-	At ave. 5 yr (1-12) = 14%
Radiofrequency thermocoagulation rhizolysis (PRFR) <sup>29</sup>	Initial = 97.6% At 5 yr = 57.7% At 10 yr = 52.3% At 20 yr = 41%	n/s	At ave 5.7±5.5 yr, recurrence rate = 25.1%
Balloon compression (PBC) <sup>30</sup>	98% procedures conducted with immediate pain relief	1.8%	At first 5 yr = 19.2% At 10.7 yr (mean) = 31.9%

<sup>1</sup> "Technical failure" in this context refers to malfunctions occurring with the equipment or errors resulting from a lack of operator skill or experience.

<sup>1</sup> The National Centre for Stereotactic Radiosurgery had performed GKS on 205 patients since the gamma knife unit was installed in October 1985. Only 15 patients had repeat treatment. No other risks apart from numbness was recorded (personal conversation with Mr Andras Kemeny, neurosurgeon, 23<sup>rd</sup> January, 2004).

## **Clinical efficacy in multiple sclerosis-TN patients and atypical TN patients**

Available evidence on multiple sclerosis TN and atypical TN patients suggests that they have less favourable pain outcomes than patients with typical TN.

For GKS, a number of studies showed that multiple sclerosis<sup>21,22,138</sup> and atypical TN<sup>10,11,13,18,138</sup> patients had less pain relief than typical TN patients. Pain recurrence rates for the multiple sclerosis patients are also higher (43%) than those for typical TN patients (13%) and those patients who suffered from atypical TN (33.3%)<sup>21</sup>. Atypical TN patients experienced a lower initial success rate<sup>10</sup> and response rate (9%) compared to patients with typical TN (49%) ( $p=0.04$ )<sup>11</sup>. The unpublished data<sup>138</sup> revealed that MS-TN patients experienced better pain relief than atypical TN patients (50% versus 0% achieved complete pain relief respectively) and only one of four atypical TN patients experienced at least 50% improvement in their pain control while the remaining three patients achieved less than 50% pain improvement (Appendix 5).

There are three studies<sup>31,76,77</sup> (Appendix 6) which compare the results of typical TN with atypical TN patients, and MS-TN with typical TN patients. These studies reported the findings after MVD and PBC treatments. Patients were found to experience pain relief at varying degrees depending on the type of treatments.

Under the MVD treatment<sup>31</sup>, atypical patients did not respond as well as typical TN patients. The PBC study<sup>77</sup> however reported that both typical and atypical patients experienced good pain relief. Mizuno and colleagues<sup>77</sup> conducted PBC on 9 typical and 6 atypical TN patients. 7/9 of the typical TN patients and 3/6 of the atypical TN patients experienced complete pain relief, without the use of medication. The other three atypical TN patients achieved at least 50% pain relief. Pain recurred in only two patients, one of which was an atypical TN patient.

There are another seven studies that briefly mentioned their findings on MS-TN<sup>76</sup> and atypical TN<sup>42-48</sup> and these studies also reported that atypical TN and MS-TN patients experienced less pain relief than patients with typical TN.

On the method of treatment, Resnick and others<sup>76</sup> treated 3 MS-TN patients with MVD alone and two others with MVD and partial rhizotomy/section of the trigeminal nerve. They found that the patients who also had partial rhizotomy along with MVD experienced better pain relief than those who only had MVD. The former achieved complete pain relief with one patient on carbamazepine while the other did not need any medication. Two of the three patients with MVD alone had recurrence at 23 and 24 months after treatment while the remaining patient was a failure at four months. It was suggested that MVD is not adequate to provide effective relief of pain for the MS-TN patients.

## **Clinical efficacy summary**

There are limitations concerning the extent to which this data can support robust extrapolations (see Chapter 3), however, it would appear that:

- none of the techniques provide long-term cure.
- all techniques produced effective initial pain relief.
- pain recurrence for GKS is lower compared to PGR, PRFR and PBC but higher than MVD.
- multiple sclerosis TN patients had less favourable pain relief outcomes and higher pain recurrence rates than those with typical TN in all techniques.

- atypical TN patients also had less favourable pain relief than patients with typical TN.

## Safety

### Complications after GKS

Appendix 7 lists the types of complications by the number of cases reported in the 23 case series reviewed and Table 5 summarises these data. Specific and general terms were used to describe complications due to the treatment. A total of 1,757 patients were treated in the 23 case series studies.

Specific types of complications reported in the 23 case series :

1. paraesthesias (tolerable and bothersome) in five studies<sup>9,15,18,19,24</sup>.
2. dysaesthesias (bothersome) in two studies<sup>9,22</sup>.
3. loss of taste in one study<sup>8</sup>.
4. corneal numbness in two studies<sup>6,9</sup>.
5. hypaesthesias in one study<sup>12</sup>.
6. thermal/algescic sensation impairments in one study<sup>21</sup>.
7. deafness in two studies<sup>13,18</sup>.

In some series, more general terms were used to describe the specific side effects listed above:

1. trigeminal nerve deficits/facial numbness in eleven studies<sup>6,8-11,13,19,20,24,27,138</sup>.
2. new/worsened trigeminal nerve dysfunction in three studies<sup>6,9,10</sup>;
3. paraesthesias and/or numbness (new/increased, minor) in two studies<sup>7,18</sup>;
4. Other cranial nerve deficits in one study<sup>24</sup>.

**Table 5 - Complications after GKS treatment**

Complications	No. of patients (%)
<b>Specific terms :</b>	
Paraesthesias (tolerable and bothersome)	33 (1.9%)
Dysaesthesias (bothersome)	24 (1.4%)
Loss of taste	7 (0.4%)
Corneal numbness	6 (0.34%)
Hypaesthesias (temporary vs. permanent)	5 (0.28%)
Thermal/algescic sensation impairments	5 (0.28%)
Deafness	2 (0.1%)
<b>General terms :</b>	
Trigeminal nerve deficits/facial numbness	139 (7.9%)
New/worsened trigeminal nerve dysfunction	66 (3.7%)
Paraesthesias and/or numbness (new/increased, minor)	39 (2.2%)
Other cranial nerve deficits	2 (0.1%)

Paraesthesia is the most frequently cited specific complication of GKS treatments reported by 33 of 1,757 patients (1.9%) in five studies after GKS treatment (Table 3). This is followed by bothersome dysaesthesias (1.4%) reported by Pollock and colleagues<sup>9</sup> and Brisman and

Mooij<sup>22</sup>, while the specific type of complication that is least observed is deafness (0.1%), found only in the study by Maesawa and others<sup>13</sup> and Kondziolka and others<sup>18</sup>.

Eleven studies used general terms to describe the complications arising from the treatment<sup>6,8-11,13,19,20,24,27,138</sup>. In this classification, the most common complication reported is trigeminal nerve deficits/facial numbness, 7.9%, followed by new/worsened trigeminal nerve dysfunction (3.7%), paraesthesias and/or numbness (2.2%) and other cranial nerve deficits (0.1%).

None of the studies reported anaesthesia dolorosa and mortality due to GKS treatment.

Kondziolka and colleagues in both studies<sup>14,16</sup> found temporary increased facial paraesthesias and decreased sensation which resolved completely after six weeks. Kannan and others<sup>26</sup> however did not observe any complication in the ten months of follow-up.

The study at the National Centre for Stereotactic Radiosurgery observed only one complication (facial numbness) in a follow up the median duration of which was eleven months<sup>138</sup>.

### **Complications compared with MVD, PGR, PRFR and PBC**

Death or disabling stroke was not found after GKS, PGR, PRFR or PBC treatments, but was for MVD. Operative mortality after MVD was as high as 14%. Non-fatal but disabling neurologic morbidity secondary to brainstem infarction, cerebellar haemorrhage, supratentorial infarction and haematomas and air embolism were also reported in the other large case series on MVD<sup>97,117,121</sup>. Sindou and others<sup>28</sup> reported disabling neurologic morbidity, i.e. ischaemic syndrome.

Anaesthesia dolorosa was reported after PGR (0 - 2%, but could be as high as 5%), PRFR (0 - 3.4%) and PBC (1 incidence) and none was reported in patients who underwent GKS and MVD. Table 6 summarised the type of neurological deficits resulting from GKS, PGR, PRFR, PBC and MVD.

**Table 6 Percentage of patients suffering from neurological complications after treatment for TN**

Type of neurological complication	GKS	PGR	PRFR	PBC	MVD
Mortality	0	0	0	0	0 - 14
Anaesthesia dolorosa	0	0 - 2	0 - 3.4	1 case	0
Dysaesthesia	1.4	na	5.2 - 24	6.7 - 8.5	0 - 2.4
Hypaesthesia	0.29	na	-	-	6 - 14
Paraesthesia	1.9	na	20	-	8
Corneal hypaesthesia	0.35	na	-	-	1.76
Hearing loss	0.14	na	less than 1	-	0 - 8
Loss of taste	0.4	-	-	-	-
Thermal/algescic sensation impairments	0.29	-	-	-	-
Masseter weakness	-	Na	less than 10.5	3	-

The percentage incidence of neurological deficits reported after GKS treatment was 0.29% - 1.9%, with hypaesthesia and thermal/algescic sensation impairments as the lowest and paraesthesias being the highest deficit reported. The types of neurological deficits reported after GKS are dysaesthesia, hypaesthesia, paraesthesia, corneal hypaesthesia, hearing loss, loss of taste, and thermal/algescic sensation impairments. Hearing loss was minor for GKS (0.14%) compared to a much higher incidence of 8% for MVD.

Available data showed that for dysaesthesia, 5.2 - 24% suffered from this type of pain after PRFR treatment, 6.7 - 8.5% after PBC and 0 - 2.4% after MVD, compared to a lower figure of 1.4% reported after GKS. Only 0.29% of GKS patients reported hypaesthesia compared to 6 - 14% of patients who underwent the MVD procedure. For paraesthesia, 1.9% of patients suffered from this pain compared to 20% after PRFR and 8% after MVD.

Masseter weakness (pain involving the masseter muscle near the jaws) was reported in less than 10.5% of PRFR patients and in 3% of those who had PBC while this was not found in the other techniques.

No surgical wound problems or muscle related weakness were reported following GKS treatment. Only MVD produced major surgical wound problems that required re-operation (Table 7). PRFR was also found to cause cerebrospinal fluid leak (0.13%) and aseptic meningitis (0.6%)<sup>29</sup>.

**Table 7 Details of complications after MVD, PRFR, PGR and PBC treatments**

Reference, type of surgical procedure	Complications
Glycerol rhizolysis (PGR) <sup>2</sup>	<ul style="list-style-type: none"> <li>- Anaesthesia dolorosa = 0-2% but could be as high as 5%.</li> <li>- paraesthesias, dysaesthesias, anaesthesia dolorosa, corneal hypaesthesia/ anaesthesia, diminished corneal reflex, neuromyolytic keratitis, masticatory muscle weakness, herpes labialis, haemotoma at the needle entry side.</li> <li>- Mortality = 0%</li> </ul>
Radiofrequency thermocoagulation rhizolysis (PRFR) <sup>2</sup>	<ul style="list-style-type: none"> <li>- Anaesthesia dolorosa = 0-3.4%</li> <li>- Reduction/loss of facial sensation in direct proportion to lesion temperature is <math>\leq 80\%</math>.</li> <li>- Post-op. paraesthesias = 20%</li> <li>- Dysaesthesias = 5.2 - 24%</li> <li>- Unwanted V<sub>1</sub> anaesthesia = 3%</li> <li>- Keratitis = 0.5-3%</li> <li>- Herpes labialis, diminution of hearing &amp; oculomotor palsy = <math>\leq 1\%</math></li> <li>- Minor masticatory weakness = <math>\leq 10.5\%</math></li> <li>- unsuspected intracranial (temporal lobe) lesions.</li> <li>- Mortality = 0%</li> </ul>
Ganglion compression /Balloon compression (PBC) <sup>2</sup>	<ul style="list-style-type: none"> <li>- Anaesthesia dolorosa = 1 incidence</li> <li>- Dysaesthesias = 6.7-8.5%</li> <li>- Masseter weakness (permanent) = 3%</li> </ul>
Microvascular decompression (MVD) <sup>2</sup>	<ul style="list-style-type: none"> <li>- Total frequency quoted by large series = 10-19%</li> <li>- Herpes labialis = 0-50%</li> <li>- Transient cranial nerve deficits with a 4% frequency, lasting 6 week to 5 yrs, facial=78%, vestibulocochlear nerve = 22%</li> <li>- Permanent cranial nerve deficit = 5.6-10%</li> <li>- Hypaesthesia = 6-14%</li> <li>- Paraesthesias = 8%</li> <li>- Dysaesthesias = 0-2.4%</li> <li>- Corneal hypaesthesia = 1.76%</li> <li>- Frank anaesthesia = 0 - 0.5%</li> <li>- Transient diplopia secondary to abducens nerve involvement = 0.8-2.7%</li> <li>- facial paresis (permanent &amp; transient) = 0.4 - 2.8%</li> <li>- minor hearing loss = 0-6%</li> <li>- major hearing loss = 0-8%</li> <li>- cerebrospinal fluid leakage = 0-2.8%</li> <li>- Operative mortality = 0-14%</li> </ul>
Microvascular decompression Sindou, 2000 <sup>31</sup>	<p><b>Neurological (%)</b></p> <p>Ischaemic syndrome (superior cerebellar artery territory- 2 patients with death and 2 patients with permanent deficits) = 0.7</p> <p>Venous congestion/oedema (severe)= 0.2</p> <p>Facial weakness(permanent) = 0.3</p> <p>Hearing loss - transient=1.4</p> <p>Hearing loss - permanent =0.3</p> <p>Trochlear nerve palsy - transient=1.2</p> <p>Trochlear nerve palsy - permanent= 0.3</p> <p>Trigeminal hypaesthesia - dysaesthesia=1.6</p> <p>Greater occipital neuralgia = 0.3</p> <p><b>Surgical wound (%)</b></p> <p>CSF leak =17.0</p>

	Bacteria meningitis (cured by antibiotics)=3.1 Serohaemorrhagic 'otitis' (with transient hearing decrease due to liquid in mid ear) = 9.9 Delayed wound healing (with need for reoperation)=0.6
Radiofrequency thermocoagulation rhizolysis (PRFR) <sup>29</sup>	- Anaesthesia dolorosa = 0.8% - Painful dysaesthesia = 1% - Absent corneal reflex = 5.7% - Corneal keratitis = 0.6% - Masseter paraesis = 3.0% - Masseter paralysis = 1.1 - Transient cranial nerve paralysis = 0.75% - Permanent cranial nerve paralysis (abducens nerve) = 0.13% - Cerebrospinal fluid leak = 0.13% - Carotid-cavernous fistula = 0.06% - Aseptic meningitis = 0.06%
Balloon compression (PBC) <sup>30</sup>	- early tolerated facial numbness = 89% - permanent facial numbness = 4.6% - symptomatic dysaesthesia = 3.8% - temporary symptomatic masseter weakness = 3.4% - temporary diplopia secondary to cranial nerve dysfunction = 1.6% - corneal anaesthesia and anaesthesia dolorosa and aseptic meningitis = 0 - 1 case, the balloon was dislodged from the end of the catheter, most likely catching and then tearing on the needle (no untoward symptoms)

**Technical failures (malfunctions occurring with the equipment or errors resulting from a lack of operator skill or experience)**

No technical failure was reported under GKS treatment, whereas this was not the case with PBC, PGR and PRFR. The figure reported for PBC was as high as 20% at 6 months and 30% at 12 months; 15% for PGR; and 6% - 7% for PRFR (Table 5). Zero technical failure was reported for MVD although operative mortality was high.

**Clinical safety summary**

To summarise, the clinical evidence on complications suggests that,

- There is indirect evidence of low neurological complication risk compared to PGR, PRFR, PBC and MVD.
- GKS has a zero rate of technical failure and a zero rate of mortality compared to a high technical failure rate in PRFR, PBC and PGR.
- GKS, PRFR, PBC and PGR have a zero rate of operative mortality and a zero rate of disabling neurologic morbidity, unlike in MVD.
- GKS, PGR and PBC do not produce any surgical wound infections, unlike MVD and PRFR.

## Chapter 3 Limitations

### Quality of studies

All the studies identified in this review are case series (although given the possibility of overlap between some of the case series the number of truly independent studies may be small), including those on PGR, PRFR, PBC and MVD in the literature review by Moore and Burchiel<sup>2</sup>. In the latter, the authors cautioned readers regarding the problems of variation in the definition of ‘good’ pain outcome, variation in the length of the follow-up period and patient population characteristics, and the experience of the neurosurgeons involved amongst the studies.

There are several other issues which limit the conclusions that can be drawn. The case-series reviewed do not have direct (head-to-head) comparisons between the alternative treatments, and although indirect comparisons have been shown to give reliable results in some circumstances, differences in case-mix due to differences in selection of patients for treatment mean that the comparative data presented here may not be reliable.

### Different radiation dosage - radiation dosage dilemma

Direct comparison or analysis between or amongst studies is made difficult by the different radiation dosage used by different neurosurgeons<sup>6,7,11,14,17</sup>. Radiation doses vary from as low as 35Gy to as high as 90Gy. Two studies in this review examined the dose escalation effect on pain outcomes and risk<sup>6,14</sup>. Pollock and others<sup>6</sup> found that a higher radiation dose at 90Gy is associated with better pain relief. Pollock and colleagues<sup>6</sup> used 70Gy and 90Gy on 27 and 43 patients respectively (mean follow-up period was 14.4 months). They not only found a trend towards improvement of facial pain outcomes and fewer patients requiring later surgery with 90Gy ( $p=0.01$ ) but they also found that the complication rate in this group (90Gy) is greater than in those who received 70Gy ( $p=0.05$ ).

In the study by Kondziolka and colleagues<sup>14</sup> they used 60Gy, 65Gy, 70Gy, 75Gy, 80Gy and 90Gy on a total of 50 patients with a mean follow-up period of 18 months. The results showed that a maximum dose of 70Gy had the greatest pain relief compared to the other dosages used.

In another study by Rogers and colleagues<sup>11</sup> who used low radiation doses of 35Gy and 40Gy, 89% of the patients achieved at least 50% pain relief but the actuarial data based on Kaplan-Meier analysis for 2.5 years on pain recurrence was 36%.

Varying maximum doses were given to different patients within the same study<sup>2,14-18,10</sup> and this made it difficult to compare outcomes of these studies.

### Different target area of radiation and length of nerve to target - target area dilemma

There also seems to be a relationship between the target area to be irradiated and the pain relief achieved. Different locations of the nerve for the GKS target are used at different

centres. Targeting the cisternal portion of the nerve was proposed by Rand et al<sup>35</sup>. The alternative is to target the gasserian ganglion, either in its retrogasserian part of the dorsal root entry zone (DREZ, see figure 1) or by direct targeting of the DREZ<sup>7</sup>. The theoretical argument is that a stronger radiobiological effect would occur at the proximal nerve where there was central oligodendrocyte myelin which is more sensitive to irradiation than the distal nerve<sup>7,14</sup>. Other techniques were proposed and used. Regis and others<sup>7</sup> argued for the target area to be closer (slightly anterior) to the retrogasserian portion than to the dorsal root entry zone (DREZ).

The radiation target zone at both the trigeminal nerve and brainstem varied in the studies in this review. In some studies, information on the target area being irradiated is not given. In those studies that provided this information, a different isodose line was used, ranging from 20% - 50%.

All the studies, except one, applied a single 4-mm isocentre. In this study, Flickinger and others<sup>19</sup> used two isocentres and found that irradiating a longer nerve length with a second isocentre did not improve the pain relief appreciably but it did increase the complications.

Different radiation dosages and target areas are used in different GKS centres. Regis and colleagues<sup>7</sup> argued for lower doses of radiation for elderly patients with multiple sclerosis and higher doses of radiation for patients with multiple prior surgeries.

## **Patient characteristics - history of prior surgery**

Patient clinical profile is an important factor in the success of the GKS treatment in relieving pain. Numerous studies showed that patients who have not had surgery before GKS treatment had better pain outcomes than those who had prior surgery<sup>7,10,15,17,18,21,22,23</sup>. 70% of patients who did not have any surgery prior to GKS treatment maintained complete pain relief at nine months and also at five years in the study by Kondziolka and others<sup>18</sup>. This group of patients also did not show any pain recurrence after nine months. These studies point to the effectiveness of gamma knife surgery as the primary management of trigeminal neuralgia rather than as a corrective treatment to prior surgery that failed.

## **Patient characteristics - clinical**

Even though target positioning was the same in the series, for example Pollock et al<sup>6</sup> and Regis et al<sup>7</sup>, the patient population and the amount of radiation delivered differed in both series. In many studies, even though the authors specified patients by types of TN (typical/essential, MS and atypical), the findings were discussed in general and not analysed by category or grouping of patients. Duration of pain<sup>9,10</sup>, number of trigeminal divisions<sup>11,17</sup>, age<sup>17</sup> and sex<sup>17</sup> were other factors that some studies in this review were concerned with.

## **Different definitions of pain levels**

There are no standard or common definitions used to describe the levels of pain control/relief achieved. In most studies, “excellent pain relief” means complete, 100% pain relief without the need for medication<sup>6,9-11,14-20,22-27</sup>. In one study<sup>8</sup>, “excellent pain outcome/relief” includes

patients who no longer need medication, those who continue with low dosage of medication and those who continue with medication for fear that the pain will recur. In another study, Urgosik and colleagues<sup>21</sup>, pain outcome was defined as residue of pain (pain which remained after treatment). There is also uncertainty about the validity of the pain assessment used in most studies, and details about issues such as pain frequency, duration, intensity and type have not usually been addressed. However, the outcome which we have focused on has been self-reported pain relief, i.e., the change in self-reported pain, and this may be fairly robust against the validity of the method of assessment.

## **GKS model type**

A different gamma knife model unit was used in different studies. Model B unit has a greater radiation volume in the left-right dimension<sup>22</sup> and the Model U unit in the superior-inferior dimension<sup>17</sup>. However, no significant correlation was found in the relationship between gamma knife models A and U with respect to pain relief<sup>17</sup>. The available data from the 22 studies showed that while different models were used none, except one study<sup>17</sup>, analysed their results by model type. Models A and B were used in two studies<sup>13,18</sup>. Model B was used in six studies<sup>9,14,20,22,23,24</sup>. Both Model U and B were used in two studies<sup>17,25</sup>.

## **Expertise/skills in planning the treatment**

Differences in results could also be due to the skills in planning the treatment, i.e. radiation dose and target area or zone. Although none of the studies reported any technical failure, pain outcome achievements, pain recurrence and complication rates vary amongst the GKS centres. Kannan and others<sup>26</sup> reported no complications in the 10 months of follow-up on their 7 patients. Many studies reported minor facial numbness or paraesthesia<sup>6-11,13,18,19,20,24,27,138</sup>.

## **Length of follow up and size of patient population**

The length of follow-up in these studies and the patient population make-up and size are not long or big enough to conclusively argue for a better or worse clinical efficacy and safety. Some studies<sup>10,13,17,23</sup> in this review have a patient size over 100 but the length of follow-up was less than 2 years on average.

## Chapter 4 Conclusion

Overall, the available evidence suggests, that on the grounds of clinical efficacy, gamma knife radiosurgery achieves good pain relief at initial follow-up. Direct comparisons with other treatments - microvascular decompression, percutaneous glycerol rhizolysis, percutaneous radiofrequency thermocoagulation rhizotomy and percutaneous balloon compression – have not been made. Indirect comparisons, based on the four case-series reviewed here, suggest that short-term outcomes are similar to those achieved by other treatments. Data on long-term outcomes are lacking.

Evidence on the safety aspect indicates that gamma knife radiosurgery produces few complications, and indirect comparisons suggest that it produces fewer complications than the other treatment techniques (MVD, PGR, PRFR and PBC) which tend to score high on some complications. The complications tend to be minor, and no death and technical failures were reported after GKS treatment. There is also a zero rate of non-fatal, disabling neurologic morbidity secondary to brainstem infarction, cerebellar haemorrhage, supratentorial infarction and haematomas and air embolism in GKS, PBC, PGR and PRFR treatments. High operative mortality rates were found only with MVD treatment and technical failure rates also tend to be high in PRFR, PBC and PGR treatments.

Comparison between studies of gamma knife radiosurgery for the treatment of trigeminal neuralgia is difficult due to the variation found on radiation dosage, radiation target area, patient sample and length of follow-up. Comparisons with other treatments to assess the relative safety and efficacy of GKS may be unreliable due to the lack of comparative trials.

There is a need for randomised controlled trials to make reliable comparisons between treatments, which also take into consideration all the issues concerning the radiation doses, radiation target area/zone, patient profiles, definition of pain outcomes, gamma knife model unit and length of follow-up period. Available evidence suggests that the choice of surgical procedure is determined by the availability of the equipment and the expertise involved. On the latter, available evidence also suggests that there is a learning curve i.e. best results and fewer complications come with experience<sup>2</sup>. Future research should also examine patient choice.

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# Appendix 1 Databases Searched and search strategies

## List of electronic bibliographic databases searched

1. BIOSIS
2. Cochrane Controlled Trials Register (CCTR)
3. Cochrane Database of Systematic Reviews (CDSR)
4. CRD Databases (DARE, NHS EED, HTA)
5. Current Controlled Trials
6. Embase
7. Medical Research Council (MRC) Clinical Trials Register
8. Medline
9. National Research Register
10. PreMedline
11. Science Citation Index
12. Tripdatabase

## 'Gamma Knife Radiosurgery'

### BIOSIS (SilverPlatter WebSPIRS, 1985 - May 2003)

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 or/1-7
- #9 gamma knife
- #10 radiotherap\*
- #11 radiation therap\*
- #12 radiation treatment\*
- #13 radiation surger\*
- #14 radiosurger\*
- #15 stereotactic radiosurger\*
- #16 stereotactic surger\*
- #17 cobalt radioisotope\*
- #18 cobalt 6
- #19 or/9-18
- #20 8 and 19

### CCTR and CDSR (The Cochrane Library, Update Software (Online version) - May 2003)

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 TRIGEMINAL NERVE DISEASES explode tree 1 (MeSH)

- #9 FACIAL NEURALGIA single term (MeSH)
- #10 FACIAL PAIN single term (MeSH)
- #11 or/1-10
- #12 gamma knife
- #13 radiotherap\*
- #14 radiation therapy
- #15 radiation therapies
- #16 radiation treatment\*
- #17 radiation surger\*
- #18 radiosurger\*
- #19 stereotactic radiosurger\*
- #20 stereotactic surger\*
- #21 cobalt radioisotope\*
- #22 cobalt 6
- #23 RADIOSURGERY single term (MeSH)
- #24 or/12 - 23
- #25 11 and 24

**CRD Databases (NHS DARE, EED, HTA - CRD website. Complete databases - May 2003)**

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 or/1-7
- #9 gamma knife
- #10 radiotherap\*
- #11 radiation therap\*
- #12 radiation treatment\*
- #13 radiation surger\*
- #14 radiosurger\*
- #15 stereotactic radiosurger\*
- #16 stereotactic surger\*
- #17 cobalt radioisotope\*
- #18 cobalt 6
- #19 or/9-18
- #20 8 and 19

**Embase (SilverPlatter WebSPIRS 1980 - May 2003)**

- #1 explode 'trigeminal nerve disease' / all subheadings
- #2 trigeminal nerve dis\*
- #3 trigeminal neu\*
- #4 idiopathic neuralgia
- #5 tic dolo?reux
- #6 neuralgia epileptiforme
- #7 explode 'facial nerve disease' / all subheadings
- #8 fac\* nerve dis\*
- #9 fac\* neuralgia
- #10 'face pain' / all subheadings
- #11 fac\* pain\*
- #12 or/1-11
- #13 ('gamma knife radiosurgery' / all subheadings) or ('gamma knife' / all subheadings)
- #14 gamma knife
- #15 explode 'radiotherapy' / all subheadings
- #16 radiotherap\*
- #17 radiation therap\*
- #16 radiation treatment\*

- #17 radiation surger\*
- #18 radiosurger\*
- #19 'stereotaxic surgery' / all subheadings
- #2 stereotaxic surger\*
- #21 stereotactic radiosurger\*
- #22 stereotactic surger\*
- #23 cobalt radioisotope\*
- #24 cobalt 6
- #25 or/13-24
- #26 12 and 25

**Medline (Ovid 1966 - May 2003)**

- #1 exp Trigeminal Nerve Diseases/
- #2 trigeminal nerve dis\$.tw
- #3 trigeminal neu\$.tw
- #4 idiopathic neuralgia.tw
- #5 tic dolo?reux
- #6 neuralgia epileptiforme.tw
- #7 Facial Neuralgia/
- #8 fac\$ neuralgia.tw
- #9 Facial Pain/
- #10 fac\$ pain\$.tw
- #11 or/1-10
- #12 gamma knife.tw
- #13 exp Radiotherapy/
- #14 radiotherap\$.tw
- #15 radiation therap\$
- #16 radiation treatment\$.tw
- #17 radiation surger\$.tw
- #18 radiosurger\$.tw
- #19 stereotactic radiosurger\$.tw
- #20 stereotactic surger\$.tw
- #21 cobalt radioisotope\$.tw
- #22 cobalt 6.tw
- #23 or/12 - 22
- #24 11 and 23

**Pre-Medline (Ovid May 9th, 2003)**

- #1 trigeminal nerve dis\$.tw
- #2 trigeminal neu\$.tw
- #3 idiopathic neuralgia.tw
- #4 tic dolo?reux
- #5 neuralgia epileptiforme.tw
- #6 fac\$ neuralgia.tw
- #7 fac\$ pain\$.tw
- #8 or/1-7
- #9 gamma knife.tw
- #10 radiotherap\$.tw
- #11 radiation therap\$
- #12 radiation treatment\$.tw
- #13 radiation surger\$.tw
- #14 radiosurger\$.tw
- #15 stereotactic radiosurger\$.tw
- #16 stereotactic surger\$.tw
- #17 cobalt radioisotope\$.tw
- #18 cobalt 6.tw
- #19 or/9 - 18
- #20 8 and 19

### **Science Citation Index (Web of Science 1981 - May 2003)**

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 or/1-7
- #9 gamma knife
- #10 radiotherap\*
- #11 radiation therap\*
- #12 radiation treatment\*
- #13 radiation surger\*
- #14 radiosurger\*
- #15 stereotactic radiosurger\*
- #16 stereotactic surger\*
- #17 cobalt radioisotope\*
- #18 cobalt 6
- #19 or/9-18
- #20 8 and 19

### **'MVD and Percutaneous Techniques'**

#### **BIOSIS (*SilverPlatter WebSPIRS, 1985 - May 2003*)**

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 or/1-7
- #9 microvascular decompression\*
- #10 mvd
- #11 percutaneous technique\*
- #12 glycerol rhizolysis
- #13 balloon compression\*
- #14 radiofrequency thermocoagulation\*
- #15 or/9-14
- #16 8 and 15

#### **CCTR and CDSR (*The Cochrane Library, Update Software (Online version) - June 2003*)**

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 TRIGEMINAL NERVE DISEASES explode tree 1 (MeSH)
- #9 FACIAL NEURALGIA single term (MeSH)
- #10 FACIAL PAIN single term (MeSH)
- #11 or/1-10
- #12 microvascular decompression\*
- #13 mvd
- #14 percutaneous technique\*

- #15 glycerol rhizolysis
- #16 balloon compression\*
- #17 radiofrequency thermocoagulation\*
- #18 or/12-17
- #19 11 and 18

**CRD Databases (NHS DARE, EED, HTA -CRD website. Complete databases - June 2003)**

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 or/1-7
- #9 microvascular decompression\*
- #10 mvd
- #11 percutaneous technique\*
- #12 glycerol rhizolysis
- #13 balloon compression\*
- #14 radiofrequency thermocoagulation\*
- #15 or/9-14
- #16 8 and 15

**Embase SilverPlatter WebSPIRS 1980 - June 2003**

- #1 explode 'trigeminal nerve disease' / all subheadings
- #2 trigeminal nerve dis\*
- #3 trigeminal neu\*
- #4 idiopathic neuralgia
- #5 tic dolo?reux
- #6 neuralgia epileptiforme
- #7 explode 'facial nerve disease' / all subheadings
- #8 fac\* nerve dis\*
- #9 fac\* neuralgia
- #10 'face pain' / all subheadings
- #11 fac\* pain\*
- #12 or/1-11
- #13 microvascular decompression\*
- #14 mvd
- #15 percutaneous technique\*
- #16 glycerol rhizolysis
- #17 balloon compression\*
- #18 radiofrequency thermocoagulation\*
- #19 or/13-18
- #20 12 and 19

**Medline, Ovid 1966-23**

- #1 exp Trigeminal Nerve Diseases/
- #2 trigeminal nerve dis\$.tw
- #3 trigeminal neu\$.tw
- #4 idiopathic neuralgia.tw
- #5 tic dolo?reux
- #6 neuralgia epileptiforme.tw
- #7 Facial Neuralgia/
- #8 fac\$ neuralgia.tw
- #9 Facial Pain/
- #10 fac\$ pain\$.tw

- #11 or/1-10
- #12 microvascular decompression\$.tw
- #13 mvd.tw
- #14 percutaneous technique\$.tw
- #15 glycerol rhizolysis.tw
- #16 balloon compression\$.tw
- #17 radiofrequency thermocoagulation\$.tw
- #18 or/12-17
- #19 11 and 18

**Pre-Medline, Ovid June 5<sup>th</sup> 2003**

- #1 trigeminal nerve dis\$.tw
- #2 trigeminal neu\$.tw
- #3 idiopathic neuralgia.tw
- #4 tic dolo?reux
- #5 neuralgia epileptiforme.tw
- #6 fac\$ neuralgia.tw
- #7 fac\$ pain\$.tw
- #8 or/1-7
- #9 microvascular decompression\$.tw
- #10 mvd.tw
- #11 percutaneous technique\$.tw
- #12 glycerol rhizolysis.tw
- #13 balloon compression\$.tw
- #14 radiofrequency thermocoagulation\$.tw
- #15 or/9-14
- #16 8 and 15

**Science Citation Index, 1981-23, Web of Science**

- #1 trigeminal nerve dis\*
- #2 trigeminal neu\*
- #3 idiopathic neuralgia
- #4 tic dolo?reux
- #5 neuralgia epileptiforme
- #6 fac\* neuralgia
- #7 fac\* pain\*
- #8 or/1-7
- #9 microvascular decompression\*
- #10 mvd
- #11 percutaneous technique\*
- #12 glycerol rhizolysis
- #13 balloon compression\*
- #14 radiofrequency thermocoagulation\*
- #15 or/9-14
- #16 8 and 15

## Appendix 2 Reasons for excluded articles

Table of excluded studies

Reference	Reasons for exclusion
1. Pollock et al, 1999 <sup>50</sup>	follow-up period too small - 2 months
2. Young et al., 1995 <sup>58</sup>	abstract
3. Barbaro et al, 2001 <sup>57</sup>	abstract
4. Ma et al., 2000 <sup>61</sup>	eye lens dose - phatom studies and in vivo measurements
5. Chang, et al, 2000 <sup>51</sup>	4 of 18 patients are not suffering from primary TN and were not separated from results
6. Andrews et al, 1995 <sup>52</sup>	secondary TN
7. Chang et al, 2002 <sup>54</sup>	case report
8. Vaughan et al, 2002 <sup>55</sup>	the plugging pattern of Leksell gamma knife
9. Alberico et al., 2001 <sup>56</sup>	not related
10. Lunsford et al, 2001 <sup>57</sup>	response to comments
11. Maher & Pollock, 2000 <sup>60</sup>	case report
12. Young, 2000 <sup>61</sup>	case report
13. Ma et al., 2000 <sup>62</sup>	helmet output of the gamma knife unit
14. Chang et al, 1999 <sup>63</sup>	secondary TN
15. Kinsella et al, 1985 <sup>80</sup>	not related
16. Hochman, 1998 <sup>65</sup>	case report
17. Maciewicz & Scrivani, 1997 <sup>66</sup>	comment
18. Worthington et al, 2000 <sup>67</sup>	case report
19. Lee-John YK et al, 2000 <sup>69</sup>	not related
20. de Lotbiniere et al, 1999 <sup>70</sup>	abstract
21. Hirato et al, 1998 <sup>71</sup>	abstract
22. Regis et al, 1998 <sup>72</sup>	secondary TN
23. Lindquist et al, 1991 <sup>73</sup>	comments
24. Podlyashuk EL, Kholodova, 1989 <sup>74</sup>	foreign language
25. Sweet et al, 1995 <sup>76</sup>	PRFR
26. Adams, 1989 <sup>110</sup>	discussion on MVD
27. Sweet, 1995 <sup>5</sup>	review article on MVD
28. Janetta, 1993 <sup>4</sup>	discussion on cause of TN
29. Apfelbaum, 1977 <sup>101</sup>	comparing PRFR & MVD
30. Broggi et al, 1993 <sup>40</sup>	discussion on percutaneous techniques
31. Burchiel et al, 1981 <sup>117</sup>	MVD vs. PRFR
32. Meglio & Cioni, 1989 <sup>118</sup>	MVD vs. PRFR
33. Kanpolat et al., 2001 <sup>120</sup>	PRFR
34. Ferguson et al, 1981 <sup>119</sup>	MVD vs. PRFR
35. Bederson et al, 1989 <sup>121</sup>	MVD and partial sensory rhizotomy
36. Waltz et al, 1989 <sup>122</sup>	PGR
37. Dieckmann et al, 1987 <sup>123</sup>	PGR
38. Barker et al, 1996 <sup>97</sup>	MVD
39. Lee et al, 1997 <sup>127</sup>	MVD vs. PRFR
40. Bergenheim et al., 1997 <sup>128</sup>	MVD
41. Sindou & Mertens, 1993 <sup>129</sup>	MVD
42. Eide & Stubhaug <sup>130</sup>	PGR
43. Fujimaki et al., 1990 <sup>131</sup>	PGR
44. Broggi et al, 1990 <sup>85</sup>	PRFR
45. Kondo, 2001 <sup>132</sup>	MVD
46. McLaughlin et al., 1999 <sup>133</sup>	MVD - cannot obtain article from British Library
47. Van Loveren et al., 1982 <sup>134</sup>	MVD
48. Correa et al, 1998 <sup>135</sup>	PBC

49. Saini 1987 <sup>100</sup>	PGR
50. Young, 1988 <sup>136</sup>	PGR
51. Sahni et al, 1990 <sup>137</sup>	PGR
52. Kanpolat & Savas, 2001 <sup>29</sup>	comments
53. Turnbull, 1974 <sup>92</sup>	PRFR
54. Piquer et al, 1987 <sup>98</sup>	PRFR
55. Latchaw et al, 1981 <sup>79</sup>	PRFR
56. Natarajan 2000 <sup>53</sup>	PBC
57. Lobato et al, 1990 <sup>91</sup>	PBC
58. Revuelta et al, 1993 <sup>102</sup>	PGR
59. Brown et al, 1993 <sup>89</sup>	PBC
60. Javadpour et al, 2003 <sup>112</sup>	MVD
61. Lee et al, 2000 <sup>113</sup>	MVD
62. Ogungbo et al, 2000 <sup>82</sup>	MVD
63. Jodicke et al, 1999 <sup>83</sup>	MVD
64. Burchiel et al., 1988 <sup>86</sup>	MVD
65. Piatt et al, 1984 <sup>87</sup>	MVD
66. Barba & Alksne, 1984 <sup>90</sup>	MVD
67. Puca et al., 1993 <sup>93</sup>	MVD
68. Sindou et al, 1987 <sup>94</sup>	foreign language
69. Kolluri & Heros, 1984 <sup>95</sup>	MVD
70. Sun et al, 1994 <sup>96</sup>	MVD
71. Fan et al, 2000 <sup>68</sup>	not related
72. Radatz et al, 2002	abstract
73. Pollock et al, 1997 <sup>80</sup>	abstract
74. Hitchcock et al, 1983 <sup>78</sup>	PRFR
75. Frank et al, 1985 <sup>99</sup>	PRFR - foreign language
76. Lee et al, 2000 <sup>69</sup>	not related
77. Brisman et al, 2002 <sup>103</sup>	not related
78. Tronnier VM et al., 2002 <sup>105</sup>	foreign language
79. Molina-Foncea A et al, 1998 <sup>106</sup>	foreign language
80. Sindou et al, 1987 <sup>107</sup>	not related
81. Peragut JC et al, 1991 <sup>84</sup>	MVD
82. Young, 2000 <sup>59</sup>	comments
83. Chilton 1987 <sup>81</sup>	not related - tumour patients

## Appendix 3 Evidence on gamma knife radiosurgery

**Data extraction table of studies on gamma knife radiosurgery**

Authors, year	Treatment type and radiation dosage (D), isocentre (C) Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patient - TN type, number, age mean± SD (range), male/female, ethnicity	Pain duration, type & no. prior surgery, follow-up mean (range), Outcomes	Results	Comments
Pollock et al., 2001 <sup>6</sup>	Gamma knife surgery (GKS), Model B Leksell gamma knife, output factor = 0.80, 4mm collimator  <b>D1= 70 Gy</b> <b>D2= 90 Gy</b>  <b>Design:</b> single-blind (assessors in FU), case series	Mayo Clinic, Rochester, MN (april 1997 - dec 1999)  <b>In:</b> No prior radiosurgery. <b>Out:</b> > 1 4-mm isocentre radiation & prior TN radiosurgery	<b>TN type:</b> Idiopathic TN patients and only had one 4-mm isocentre radiation <b>At beginning</b> <b>N = 102 patients</b> <b>At end</b> <b>n = 70</b> (at last F/U =68 – 1 died of unrelated causes, 1 lost to follow-up)  <b>Radiation dosage (patient no.) :</b> <b>At beginning</b> <b>D1: 27</b> <b>D2: 43</b> <b>At end:</b> <b>D1: 27</b> <b>D2: 41</b>  <b>Age: (mean/range)</b> <b>D1: 67</b> <b>D2: 68</b>  <b>M/F:</b> <b>D1: 10/17</b> <b>D2: 21/20</b>	<b>Pain duration (yr):</b> <b>D1 = 10.5</b> <b>D2 = 9.7</b>  <b>No. prior surgery before GKS (mean no.):</b> <b>D1 = 1.9</b> <b>D2 = 1.8</b>  <b>FU:</b> patients instructed to continue perioperative medications until pain was gone and then to taper medications as tolerated over an interval of few weeks. <b>Mean FU (mo) = 14.4 (2-36)</b>  <b>Primary:</b> facial pain outcomes defined as excellent (pain-free, no medications), good (pain-free, medications req. at decreased dose), fair (significantly less pain, medications req. at a decreased dose, patient would repeat procedure to obtain this level of pain control), & poor (no significant change in pain, patient would not repeat procedure to obtain this level of pain control).	<b>1) Initial facial pain outcomes</b> Pain level <b>D1</b> <b>D2</b> <b>p</b> Excellent      15(56%)      24(59%)      na Good      3(11%)      7(17%)      na Fair      5(19%)      7(17%)      na Poor      4(15%)      3(7%)      na Pain-free      18(67%)      41(76%)      0.60 Pain recurrence      7(26%)      6(15%)      na  <b>2) At last FU</b> Pain level <b>D1</b> <b>D2</b> <b>p</b> Pain-free      11(41%)      25(61%)      0.17  <b>3) Additional surgery after GKS</b> Fewer patients in D2 required additional surgery after first GKS than D1, D2<D1 = 20%<44% (p=0.05.) <b>Additional surgery</b> <b>D1</b> <b>D2</b> at median 11 mo(3-27)      12(44%)      - glycerol rhizotomy      5 repeated GKS      7 at median 5 mo (2-13)      -      8(20%) mvd      3 glycerol rhizotomy      4 peripheral alcohol blocks      1  <b>4) Complication/adverse effects</b> No other complications apart from new or worsened TN deficits (D2>D1). These deficits were temporary in 5 D2 patients and 2 D1 patients. The incidence of trigeminal nerve dysfunction at last FU for D2>D 1 and bothersome dysaesthesias in D2>D1 (13 vs 1, p=0.01). 0 patient of dysaesthesias reported any significant improvement from symptom onset.  Complications <b>D1</b> <b>D2</b> <b>p</b>	Study examining the relationship btw. radiation doses & risk.  No details of how patients scaled/assessed pain level and no details of what is meant by 'this level of pain control' by authors. Conclusion : although there is a trend toward improved facial pain outcomes in D2 and fewer D2 patients required later surgery, morbidity in D2 is > than D1. Two-thirds of D2 stated they had some degree of trigeminal dysfunction after GKS and one-third of them complained of bothersome dysaesthesias that -+vely affected their daily activities.  Authors surmised that dose selection must balance both goals of pain relief and an acceptable degree of delayed facial numbness, paraesthesias and dysaesthesias. Because if high incidence of significant trigeminal nerve dysfunction after high-dose irradiation, dose prescription for TN GKS should be limited to

				<p><b>Adverse effects:</b> complication</p>	<p>New/worsened TN deficits 6(22%) 27(66%) 0.0001 Trigeminal nerve dysfunction (15%) (54%) 0.003 Corneal numbness 0 3 -</p> <p><b>5) Pain recurrence after initially reported being pain-free (49 patients)</b> 27 out of 49 (55%) had a new trigeminal complaint after GKS. 19 with pain levels of fair or poor facial pain, 6 (32%) had a change in facial sensation (<math>p=0.14</math>). In the pain-free patients, recurrent developed in 41% (9/22) without a new deficit, vs. pain recurred in 15% (4/27) with trigeminal nerve dysfunction after GKS (<math>p=0.08</math>).</p>	<p>&lt;90Gy.  Long-term FU data needed.</p>
Regis et al, 1999 <sup>7</sup>	<p>Gamma knife surgery (GKS), Model B Leksell gamma knife, a single 4mm collimator centred on the cisternal retrogasserian part of the 5th nerve root, dose at 50% isoline=40-45Gy</p> <p><b>D=</b> 90 Gy (standard). Max range=75-90Gy</p> <p><b>Design:</b> single-blind (assessors in FU), case series</p>	<p>Marseille, France</p> <p><b>In:</b> All TN patients <b>Out:</b> -</p>	<p><b>TN type:</b> essential neuralgia</p> <p><b>At beginning</b> <b>N =</b> 75 patients</p> <p><b>At end, N=</b>57</p> <p><b>Age:</b> <b>(mean/range)</b> n/a</p> <p><b>M/F:</b> n/a</p>	<p><b>Period FU (mo) =</b> 3mo - 5yrs</p> <p><b>Primary:</b> facial pain outcomes defined as (1) pain free without medication &amp; (2) the others</p> <p><b>Adverse effects:</b> complication</p>	<p><b>1) Pain relief</b> Median time of response =4wks (1day-4 mo) <b>Pain cessation</b>                      %patients</p> <p>Initial pain relief :</p> <ul style="list-style-type: none"> <li>- pain free without drug                      87</li> <li>- only improved                                      6</li> <li>- failures    7</li> </ul> <p>Last FU :</p> <ul style="list-style-type: none"> <li>- pain free without drug                      79</li> <li>- pain relapse in those previously attained complete pain relief                      10</li> </ul> <p><b>2) Complication/adverse effects</b> No new/increased trigeminal paraesthesias or sensory loss after GKS to date.</p>	<p>Data abstraction only on essential TN and where possible MS-related and atypical TN. This study also included patients with tumour-related TN and epilepsy.</p> <p>The first 18 GKSs were conducted only with computed tomography (CT) scan localisation &amp; the Kula dosimetry system and thus not being analysed. 57 consecutive patients were treated with GammaPlan advanced dosimetry system &amp; radiological localization combining both CT scans &amp; MR imaging.</p> <p>Elderly patients with MS, multisystemic atheromatous vasculopathy or a small trigeminal cistern (nerve located close to the brain stem anteriorly) were argument for lower doses (75-85Gy).</p> <p>Unlike other studies, these authors didn't consider multiple prior surgery to be an argument for lower doses. Instead they were given higher dose (90Gy) as they had a higher risk of failure)</p> <p>Technique = a higher range of doses and target is a bit more anterior (closer to the retrogasserian portion than to the DREZ).</p> <p>Conclusion : would use the DREZ and the adjacent descending root of the trigeminal nerve as the primary surgical target and the retrogasserian area as a secondary</p>

						surgical target. Results to be confirmed by a RCT, i.e. GKS as a real alternative to other surgical methods.																								
Nicol et al., 2000 <sup>8</sup>	Gamma knife surgery (GKS), Model U, single isocentre 4-mm colliator, 20% isodose line was tangential to the brainstem resulting in a dose of 18 Gy to the margin of the pons.  <b>D1</b> = 90 Gy  <b>Design:</b> case series, single blinded	<b>In:</b> Typical TN, only patients refractory to medical management, intolerable of medication side effects <b>Out:</b> atypical facial pain, multiple sclerosis, mass lesions	<b>TN type:</b> typical TN  <b>At beginning</b> <b>N</b> = 42 <b>At end</b> <b>n</b> = 42  <b>Age:</b> <b>(mean/range)</b> <b>D1:</b> 61 (28-92)  <b>M/F:</b> <b>D1:</b> 14/28	<b>No. prior surgery before GKS:</b> 30 patients had none and 12 had 14 procedures altogether.  <b>FU:</b> information obtained fr. clinic visits and telephone calls by a trained nurse. <b>Mean FU (mo)</b> = 14 (3-30)  <b>Primary:</b> facial pain outcomes = excellent (pain free), good (> 50% improvement), failure (< 50% improvement) <b>Adverse effects:</b> complications	<b>1) pain outcomes</b> <table border="1"><thead><tr><th>Pain level</th><th>D1</th><th>p</th></tr></thead><tbody><tr><td>Excellent</td><td>31(73.8%)</td><td>na</td></tr><tr><td>Good</td><td>9(21.4%)</td><td>na</td></tr><tr><td>Failure</td><td>2(4.8)</td><td>na</td></tr></tbody></table> Majority of patients with excellent outcome no longer taking medication, 3 continue with low-dose, 1 takes carbamazepine for seizures, 2 take 200mg carbamazepine daily a.m. because of fear of pain return.  4 of 9 patients with good outcome reduced medication dosage significantly.  <b>2) Additional surgery after GKS</b> The 2 failed treatments had initial pain-free but pain recurred after. Both patients had repeated GKS with 90Gy and achieved complete pain relief.  Overall, 95% patients had good or excellent pain outcomes. Median time to pain relief = 3 wks (1-82 days)  <b>3) Complication/adverse effects</b> 7 patients (16.7%) reported new or worsened facial numbness (3 discovered only after meticulous clinical exam.). None reported problem independently or considered it bothersome. No neuropathy or anaesthesia dolorosa occurred.  4 patients reported loss/change in taste and all could identify at least 2 basic taste modalities.  <table border="1"><thead><tr><th>Complications</th><th>D1</th><th>p</th></tr></thead><tbody><tr><td>New/worsened facial numbness</td><td>7</td><td>na</td></tr><tr><td>Total loss of taste</td><td>2</td><td>na</td></tr><tr><td>Partial loss of taste</td><td>2</td><td>na</td></tr></tbody></table> No other complications observed.	Pain level	D1	p	Excellent	31(73.8%)	na	Good	9(21.4%)	na	Failure	2(4.8)	na	Complications	D1	p	New/worsened facial numbness	7	na	Total loss of taste	2	na	Partial loss of taste	2	na	Study did not compare effectiveness of use of this dosage between patients with and without prior procedures.  Only discovered problem of new facial numbness after meticulous clinical exam.  Conclusion : use of 90 Gy is safe and effective but longer FU period required to catalogue failure rate.
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Pollock et al., 2002 <sup>9</sup>	Gamma knife surgery (GKS), Model B Leksell gamma knife, 0.8 output factor for 4mm	Mayo Clinic, Rochester, MN (april 1997 - aug 2000)  <b>In:</b> medically	<b>TN type:</b> Idiopathic TN patients  <b>At beginning</b> <b>N</b> = 117 patients	<b>Pain duration (yr):</b> <b>D*</b> = 10.5 (0.5-5.5)  <b>No. prior surgery before GKS (mean):</b> <b>D*</b> = 0.9(0-4)	<b>1) Facial pain outcomes (med. time to complete pain relief = 3 wks, range 1 - 20 wks)</b> <table border="1"><thead><tr><th>Pain level</th><th>D*</th></tr></thead><tbody><tr><td>Excellent (P1)</td><td>69(59%)</td></tr><tr><td>Good(P2)</td><td>19(16%)</td></tr><tr><td>Fair(P3)</td><td>12(10%)</td></tr></tbody></table>	Pain level	D*	Excellent (P1)	69(59%)	Good(P2)	19(16%)	Fair(P3)	12(10%)	GKS more effective in patients without prior surgeries than those with prior surgeries.  Conclusions :																
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<p>collimator</p> <p><b>D1 = 70 Gy</b>  <b>D2 = 80 Gy</b>  <b>D3 = 90 Gy</b>  <b>D* = D1+D2+D3</b></p> <p><b>Design:</b> use of actuarial data</p>	<p>intractable idiopathic TN, patients with single-session of GKS only</p> <p><b>Out:</b> Tumor-related TN, multiple sclerosis TN patients</p>	<p>(8 with atypical pain)</p> <p><b>At end</b>  <b>n = 117</b></p> <p><b>Radiation dosage (patient no.) :</b>  <b>At beginning &amp; end :</b></p> <p><b>One 4 mm isocentre = 92</b>  <b>D1:27 (23%)</b>  <b>D2: 14 (12%)</b>  <b>D3: 51 (44%)</b></p> <p><b>Two 4 mm isocentres = 25</b>  <b>D1:24</b>  <b>D2: 1</b></p> <p><b>Age: (mean/range)</b>  <b>D*: 67.8 (38-91)</b></p> <p><b>M/F:</b>  <b>D*: 54/63</b></p>	<p><b>FU:</b> patients instructed to continue perioperative medications until pain was gone and then to taper medications as tolerated over an interval of few weeks. Patients were contacted routinely at 1 mo, 3 mo and then yearly. All data computerised.</p> <p><b>Mean FU (mo) = 26 (12-48)</b></p> <p><b>Primary:</b> facial pain outcomes calculated using the kaplan-meier: method - excellent (pain-free &amp; no medications), good (pain-free, &amp; reduced level of medications), fair (significantly less pain &amp; fewer medications req. &amp; patient would repeat procedure to obtain this degree of pain relief), &amp; poor (no significant change in pain &amp; medication requirement).</p> <p><b>Adverse effects:</b> complications</p>	<table border="0"> <tr> <td>Poor(P4)</td> <td>17(15%)</td> </tr> <tr> <td>Pain-free</td> <td>85(75%)</td> </tr> </table> <p><b>2)Pain recurrence</b>  <u>Pain recurrence amongst n(%)</u>  P1 at med. 8 mo (2-30 mo) 11(16)  P2 at med. 5 mo (4-25 mo) 9(47)</p> <p><b>3) At last FU (n = P1+P2 = 58+10 = 68)</b>  <u>Pain outcomes Year1 Year 3</u>  Excellent 57% 55%  Excellent or good 65% 55%</p> <p><b>4) Repeated surgeries</b>  37/68 patients (32%) has additional surgery at med. 8 mo. after GKS (1-40 mo)  <u>Additional surgeries:</u></p> <ul style="list-style-type: none"> <li>glycerol rhizotomy = 17 patients</li> <li>radiofrequency rhizotomy and balloon compression = 1</li> <li>repeated GKS = 10</li> <li>mvd = 8</li> </ul> <p><u>Pain Outcomes : Excellent</u>  Overall, 27(73%) of 37 patients achieved excellent pain outcomes due to additional surgeries after failed initial GKS</p> <ul style="list-style-type: none"> <li>glycerol rhizotomy = 12/17 patients</li> <li>radiofrequency rhizotomy and balloon compression = 1</li> <li>repeated GKS = 8/10</li> <li>mvd = 6/8</li> </ul> <p><b>5) without prior vs. with prior surgeries</b>  Multivariate analysis showed that 67% patients without prior surgery achieved and maintained excellent pain outcomes in year 1 and 3 after GKS vs. 51% of patients with prior surgeries at year 1 and 46% at year 3.</p> <p><b>6) Complication/adverse effects</b>  <table border="0"> <tr> <td><u>Complications</u></td> <td><b>D*</b></td> </tr> <tr> <td>New/worsened TN dysfunction at med. 8 mo. (2-20) onset</td> <td>43(37%)</td> </tr> <tr> <td>Numbness</td> <td>10(8%)</td> </tr> <tr> <td>Tolerable paraesthesias</td> <td>19(16%)</td> </tr> <tr> <td>Significant/bothersome dysaesthesias</td> <td>14(12%)</td> </tr> <tr> <td>- corneal numbness</td> <td>3</td> </tr> </table> </p>	Poor(P4)	17(15%)	Pain-free	85(75%)	<u>Complications</u>	<b>D*</b>	New/worsened TN dysfunction at med. 8 mo. (2-20) onset	43(37%)	Numbness	10(8%)	Tolerable paraesthesias	19(16%)	Significant/bothersome dysaesthesias	14(12%)	- corneal numbness	3	<ul style="list-style-type: none"> <li>Patients without previous surgery have significantly better outcomes than patients who had prior operations.</li> <li>new facial numbness was associated with pain relief in subsequent surgery. Authors believe that radiosurgery should be considered to be an ablative procedure whose long term success depends on the production of some degree of trigeminal dysfunction.</li> </ul> <p>Long-term FU data needed.</p>
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					<p>Other cranial nerve deficits 2</p> <p>Univariate analysis found that a radiation dose of 90Gy correlated with postradiosurgery trigeminal deficits (RR=3.10, 95%CI 1.64-5.81, p&lt;0.001). Postradiosurgery trigeminal dysfunction strongly correlated with excellent facial outcomes. Excellent outcomes of 76% at 1 and 3 years respectively after GKS were achieved and maintained in patients with new trigeminal dysfunction, vs. only 46% and 42% respectively in patients who did not experience postradiosurgery trigeminal dysfunction (RR=4.53, 95% CI 2.03-9.95, p&lt;0.01)</p> <p>Two patients suffered fr. ipsilateral problems : Ipsilateral hearing loss 1 wk after GKS (hearing return to baseline within several wks) and ipsilateral facial weakness 2 mo after GKS (facial strength improved but remained slightly abnormal 16 mo after GKS). Both patients became pain-free after operation but complication might not be due to radiation administration as it was &lt; 2 Gy, thus unlikely to be radiation-related.</p> <p><b>7) Univariate analysis revealed 3 factors to be statistically significant for achieving and maintaining an excellent outcome :</b></p> <ol style="list-style-type: none"> <li>1. younger age (p=0.04)</li> <li>2. no previous surgery (p=0.06)</li> <li>3. longer length of irradiated portion of the nerve (p=0.15).</li> </ol> <p>Other factors, i.e. pain duration, prior trigeminal deficits, presence of atypical features and radiation dose didn't correlate with excellent pain outcomes.</p> <p><b>8) Multivariate analysis revealed :</b></p> <ol style="list-style-type: none"> <li>1. patients with no prior surgery had better outcomes after GKS (RR=1.77, 95% CI 1.01-3.12, p=0.04)</li> <li>2. longer length of irradiation of the nerve and age have little association with excellent pain outcomes.</li> <li>3. a max. dose of 90Gy was associated with increased rates of trigeminal sensory disturbance</li> </ol>	
Young et al., 1998 <sup>10</sup>	Gamma knife surgery (GKS), single isocentre exposure localised to the trigeminal	<b>In:</b> Typical TN, only refractory patients to medication management TN	<b>TN type:</b> typical TN (n=106) and multiple sclerosis (n= 4) <b>At beginning</b>	<b>No. prior surgery before GKS:</b> 72 patients had none and 38 had 81 procedures altogether.	<b>1) pain outcomes</b> Initially, 97/110 (88.2%) achieved an excellent or good pain outcome. Pain recurred in 13 of 97 patients (4 had atypical features, 4 had multiple prior surgeries & 5 had typical TN without extensive history of prior surgeries) Pain level                      N                      p	GKS is an effective and safe therapy of TN. Recurrent pain are uncommon, particularly amongst patients with typical TN

	<p>sensory root so that the 40% isodose line was tangential to the pontine surface.</p> <p><b>D1</b>= 70 Gy <b>D2</b> = 80Gy</p> <p><b>Design:</b> case series, single-blinded assessators</p>	<p>with a typical features, multiple sclerosis patients</p> <p><b>Out:</b> TN due tumour</p>	<p><b>N</b> = 110 <b>(D1= 87, D2= 22 &amp;</b> 1 patient treated in 2 sessions 7 mo apart with doses 30 and 40Gy.)</p> <p><b>Age:</b> <b>(mean/range) =</b> 64.7 (33-89)</p> <p><b>M/F:</b> 75/35</p> <p>Pain duration = 3 mo-40 yr (8.1 yr)</p>	<p><b>FU:</b> information obtained by trained nurses (blinded) via mail, telephone, patient's personal physician.</p> <p><b>Mean FU (mo) =</b> 19.8 (4-49)</p> <p><b>Primary:</b> facial pain outcomes = excellent (pain free &amp; no medication), good (50% improvement &amp; small tolerable doses of medication), failure (&lt; 50% improvement &amp; no pain relief 90 days after GKS)</p> <p><b>Adverse effects:</b> complications</p>	<table border="0"> <tr> <td>Excellent</td> <td>84(76.4%)</td> <td>na</td> </tr> <tr> <td>Good</td> <td>13(11.8%)</td> <td>na</td> </tr> <tr> <td>Failure</td> <td>13(11.8%)</td> <td>na</td> </tr> </table> <p>Mean latency of pain relief = 14 days (min = 24 hrs). 42/97 (43.3%) with excellent/good outcomes achieved relief within 1 wk of treatment.</p> <p><b>2) Recurrent pain (kaplan meier analysis)</b> Recurrent pain rate dropped to 15.7% when patients with atypical pain were excluded and further reduced to 3.3% when patients with atypical features and multiple prior surgeries excluded (significant statistically at p=0.0059). That is, only 3.3% of patients with classical symptoms of TN suffered recurrent pain, for a long term success rate of 92.2%. The initial success rate is lower for patients with atypical and prior unsuccessful surgical attempts (initial pain relief in &gt;85% &amp; long-term relief abt. 70%)</p> <table border="0"> <tr> <td><u>Of all patients (110)</u></td> <td><u>recurrence rate</u></td> </tr> <tr> <td>Recurrent pain</td> <td>34%</td> </tr> <tr> <td>After exclusion of patients with:</td> <td></td> </tr> <tr> <td>    atypical pain</td> <td>15.7%,</td> </tr> <tr> <td>    atypical features and multiple prior surgeries</td> <td>3.3%</td> </tr> </table> <p><b>3) Cox regression analysis showed that</b> none of the following was statistically significant or associated with pain relief (disease duration, sex, age, and no. of prior surgeries)</p> <p><b>4) Complication/adverse effects</b></p> <table border="0"> <tr> <td><u>Complications</u></td> <td><u>patients</u></td> </tr> <tr> <td>delayed alteration to facial sensation</td> <td>3</td> </tr> <tr> <td colspan="2">(2 between 6-12 mo, one 18mo)</td> </tr> <tr> <td>worsened TN</td> <td>1</td> </tr> <tr> <td colspan="2">(patient with long history and atypical features)</td> </tr> <tr> <td colspan="2">No other complications observed.</td> </tr> </table>	Excellent	84(76.4%)	na	Good	13(11.8%)	na	Failure	13(11.8%)	na	<u>Of all patients (110)</u>	<u>recurrence rate</u>	Recurrent pain	34%	After exclusion of patients with:		atypical pain	15.7%,	atypical features and multiple prior surgeries	3.3%	<u>Complications</u>	<u>patients</u>	delayed alteration to facial sensation	3	(2 between 6-12 mo, one 18mo)		worsened TN	1	(patient with long history and atypical features)		No other complications observed.		<p>No analysis of outcome for MS-TN patients conducted by authors.</p> <p>Authors postulated that overall effectiveness of GKS similar to other surgical treatment and considerably safer, and is probably better than pharmacological treatment. They recommend that once the diagnosis of trigeminal neuralgia is established by the clinical history and initial response to carbamazepine, that early treatment with GKS be carried out. Current data indicates that this strategy will result in long-term pain relief in &gt;92% of patients.</p> <p>Long-term FU data needed.</p>
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<u>Of all patients (110)</u>	<u>recurrence rate</u>																																				
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After exclusion of patients with:																																					
atypical pain	15.7%,																																				
atypical features and multiple prior surgeries	3.3%																																				
<u>Complications</u>	<u>patients</u>																																				
delayed alteration to facial sensation	3																																				
(2 between 6-12 mo, one 18mo)																																					
worsened TN	1																																				
(patient with long history and atypical features)																																					
No other complications observed.																																					
Rogers et al, 2000 <sup>11</sup>	<p>Gamma knife surgery (GKS), 50% via single 4-mm isocentre targeting the ipsilateral trigeminal nerve next to the pons.</p>	<p>Barrow Neurological Institute (BNI) march 1997-march 1999</p> <p><b>In:</b> Typical TN, only refractory patients to</p>	<p><b>TN type:</b> typical TN (n=43), atypical pain (n= 11). 10 of 54 patients have multiple sclerosis</p> <p><b>At beginning</b></p>	<p><b>No. prior surgery before GKS:</b> 29 patients had none and 25 had &gt;=1 prior invasive treatment(s).</p> <p><b>FU:</b> evaluated by a standardised questionnaire</p>	<p><b>1) Initial pain response</b> Initially, 52/54(96%) reported improvement in pain level after GKS.</p> <table border="0"> <tr> <td><u>Initial pain level</u></td> <td><u>N(%)</u></td> </tr> <tr> <td colspan="2"><u>BNI scoring system</u></td> </tr> <tr> <td>I</td> <td>19(35)</td> </tr> <tr> <td>II</td> <td>3(6)</td> </tr> <tr> <td>III</td> <td>26(48)</td> </tr> </table>	<u>Initial pain level</u>	<u>N(%)</u>	<u>BNI scoring system</u>		I	19(35)	II	3(6)	III	26(48)	<p>GKS is an appropriate option for TN, appears to have comparative efficacy with other surgical methods and to have the most favourable side effect profile (absence of neurologic complications, anaesthesia dolorosa and</p>																					
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	<p><b>D1= 35 Gy</b> <b>D2 = 40 Gy</b></p> <p><b>Design:</b> case series</p>	<p>medication management and suffered side effects, TN with a typical features, multiple sclerosis patients <b>Out:</b> TN due tumour</p>	<p><b>N = 54(D1= 41, D2= 13 &amp; 1 patient treated in 2 sessions 7 mo apart with doses 30 and 40Gy.)</b></p> <p><b>At end : N= 53</b></p> <p><b>Age: (mean/range) = 67 (43-89)</b></p> <p><b>M/F: 33/21</b></p>	<p>filled out by patient independently at 6-mo intervals. Patients assessed pain level before GKS &amp; for each FU assessment after GKS, before &amp; after any previous invasive surgical therapy using BNI scoring system. Clinical FU at 3-6 mo intervals.</p> <p><b>Mean FU (mo) = 12 (3-28)</b></p> <p><b>Primary:</b> BNI's facial pain scores/outcomes = I (pain free &amp; no medication), II (occasional pain &amp; no medication), III (some pain, adequately controlled with medicine), IV (some pain, not adequately controlled with medicine), V (severe pain/no pain relief)</p> <p><b>Adverse effects:</b> incidence and severity of complications. BNI's facial numbness score = 1 (no facial numbness), II (mild facial numbness, not bothersome), III (facial numbness, somewhat bothersome), IV (facial numbness, very bothersome)</p>	<p>IV 4(7) V 2(4)</p> <p><b>2) Pain response timing</b> Mean latency of initial pain relief = 15 days (min &lt;=24 hrs, max = 192 days). Mean latency of maximal relief = 63 days (min= immediate, max= 253 day). 17 patients (31%) had immediate pain improvement after GKS. 9/17 had immediate pain relief at BNI score I.</p> <p><b>2) Recurrent pain</b> 11 patients had recurrent pain, the median time to recurrence = 6.7 mo (1-20 mo). The actuarial 2.5 yr pain recurrent rate for the entire patient group = 36%.</p> <p>Patients with better initial responses were less likely to develop recurrent pain. Only 1/19 patients with BNI score I pain relief developed recurrent pain. None of 3 BNI score II developed recurrent pain. 6/26 BNI score III and all 4 of score IV relief experienced recurrence.</p> <p><b>3) Complication/adverse effects</b> The only complication observed was delayed, partial facial sensory loss = 9 patients.</p> <p><b>4) univariate analysis (on response with BNI score I or II as endpoints) analysis suggests 3 variables with statistical significance :</b> - <u>no. of trigeminal divisions</u> involved may be predictive (p=0.065). Patients with pain in a single trigeminal div. had 53% response rate vs. 41% in patients with 2 trigeminal divs. &amp; 13% in patients with 3 divs. - patients with <u>typical pain features</u> had a 49% response rate vs. 9% in those with atypical pain (p=0.04) - patients with <u>new numbness</u> following GKS experienced a 100% rate of BNI score I/II vs. 35% patients with no new numbness (p=0,019).</p>	<p>morbidity).</p> <p>Long-term FU data required.</p>
Rogers et al, 2002 <sup>12</sup>	Gamma knife surgery (GKS), 50% isodose via single 4-mm isocentre	Barrow Neurological Institute (BNI) May 2002-dec 2002	<p><b>TN type:</b> multiple sclerosis</p> <p><b>At beginning N =15</b></p>	<p><b>No. prior surgery before GKS:</b> 5 patients had prior invasive treatment(s).</p>	<p><b>1) Initial pain response</b> Initially, 12(80%) experienced pain relief. 2 patients in score III were pain free but was either still tapering their medications or wished to continue pharmacological therapy and were anxious about recurrence without</p>	GKS is an effective and appealing treatment for MS-TN. It is minimally invasive and few side effects even after second procedure,

	<p>targeting the ipsilateral trigeminal nerve next to the pons.</p> <p><b>D1 = 70 Gy</b> <b>D2 = 80 Gy</b> <b>D3 = 90Gy</b></p> <p><b>Design:</b> case series</p>	<p><b>In:</b> multiple sclerosis associated TN <b>Out:</b> other TN</p>	<p><b>(D1= 7, D2= 5 &amp; D3= 3</b> (irradiation dosage increased systematically due to no adverse events observed.)</p> <p><b>At end : N= 15</b></p> <p><b>Age:</b> <b>(mean/range) = 63 (45-85)</b></p> <p><b>M/F:</b> 5/10</p>	<p><b>FU:</b> evaluated by a standardised questionnaire filled out by patient independently at 6-mo intervals. Patients assessed pain level before GKS &amp; for each FU assessment after GKS, before &amp; after any previous invasive surgical therapy using BNI scoring system. Clinical FU at 3-6 mo intervals.</p> <p><b>Mean FU (mo) = 17 (6-38)</b></p> <p><b>Primary:</b> BNI's facial pain scores/outcomes = I (pain free &amp; no medication), II (occasional pain &amp; no medication), III (some pain, continue with medication) IIIa (no pain but continue medication), IIIb (some pain, controlled with medication), IV (some pain, not controlled with medicine), V(severe pain/no pain relief)</p> <p><b>Adverse effects:</b> incidence and severity of complications. BNI's facial numbness score = 1 (no facial numbness), II (mild facial numbness, not bothersome), III(facial numbness, somewhat bothersome), IV (facial numbness, very bothersome)</p>	<p>medicine. 6 (86%) of 7 patients in score III reduced medication intake by at least 50% (this is important as high dose of drug, commonly carbamazepine, are often associated with unpleasant side effects like ataxia, which of particular concern to MS pain. 3 of 15 MS patients had no pain relief.</p> <table border="1"> <thead> <tr> <th>Initial pain level</th> <th>N(%)</th> </tr> </thead> <tbody> <tr> <td>BNI scoring system</td> <td></td> </tr> <tr> <td>I</td> <td>5</td> </tr> <tr> <td>II</td> <td>0</td> </tr> <tr> <td>III</td> <td>7</td> </tr> <tr> <td>    IIIa</td> <td>2</td> </tr> <tr> <td>    IIIb</td> <td>5</td> </tr> <tr> <td>IV</td> <td>0</td> </tr> <tr> <td>V</td> <td>3</td> </tr> </tbody> </table> <p><b>2) Pain response timing (12 patients)</b> Mean latency of initial pain relief = 13 days (1-61 days). Mean latency of maximal relief = 56 days (min= 1, max= 157 day). 2 patients had immediate pain improvement after GKS &lt;=24 hrs.</p> <p><b>2) Repeated GKS/recurrent pain (mean 48Gy, 35-80Gy)</b> 5 patients had repeated/2nd GKS. The mean interval btw 1st &amp; 2nd procedures = 534 days (231-946). Same area of the nerve was targeted. All 5 patients had attained pain relief - BNI score I (3), score IIIa (1) &amp; score IIIb (1)</p> <p><b>3) Complication/adverse effects</b> The only complication observed was delayed facial sensory loss. But all patients achieved complete pain relief &amp; ceased all medication.</p> <p>facial hypaesthesias after 1st GKS (score II)     2 faical hypaesthesias after 2nd GKS (score II)     5</p>	Initial pain level	N(%)	BNI scoring system		I	5	II	0	III	7	IIIa	2	IIIb	5	IV	0	V	3	<p>although there is a small risk of mild, delayed facial sensory loss. This minimal level of hypaesthesias may even be desirable because it appears to correlate consistently with complete pain relief appropriate option for TN,</p>
Initial pain level	N(%)																							
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Maesawa et al, 2001 <sup>13</sup>	<p>Gamma knife surgery (GKS), model A and B, Leksell Gamma Knife</p> <p><b>D = 60 - 90 Gy</b></p>	<p>University of Pittsburgh, Dec 1992-dec 1998</p> <p><b>In:</b> idiopathic TN <b>Out:</b> non-idiopathic TN</p>	<p><b>TN type:</b> idiopathic</p> <p><b>At beginning N = 220</b></p> <p><b>At end : N= 220</b></p>	<p><b>No. prior surgery before GKS:</b> 1(86 patients), 2 (39) &amp; &gt;3 (10)</p> <p><b>FU:</b> outcome data obtained fr. patients' physician and</p>	<p><b>1) Pain response timing</b> - Most patients responded to GKS within 6 mo (median=2 mo)</p> <p><b>2) Pain relief</b> - At initial FU, 82.3% (181) patients &gt; 50% pain relief (105(47.7%) had excellent result, 34 with good pain</p>	<p>Authors didn't analyse outcomes based on the different dosage irradiation (dose escalation study)</p> <p>GKS is a good choice for</p>																		

	<p><b>Design:</b> case series</p>	<p>(multiple sclerosis, tumour and secondary TN, and patients who have undergone repeated GKS.</p>	<p><b>(Dosage)% patients</b> 60Gy(2.7%), 70(24.1%), 75(21.8%), 80(48.6%), 85(1.8%), 90Gy(0.9%)</p> <p><b>Age: (mean/range) =</b> 70 (26-92)</p> <p><b>M/F:</b> 94/126</p>	<p>telephone.</p> <p><b>Mean FU (mo) =</b> 24 (maximum=6.5)</p> <p><b>Primary:</b> latency of patients' response, length and durability of pain relief. Pain outcomes = excellent (complete pain free without medication), good (complete pain-free but still need medication), fair (partial pain relief (&gt;=50%), poor (&lt;50% pain relief) - decided by patients.</p> <p><b>Adverse effects:</b> complications</p>	<p>outcomes, 42 with fair outcomes.)</p> <ul style="list-style-type: none"> <li>- At last FU, 69.1%(152) patients achieved &gt; 50% pain relief (88=excellent outcome, 33=good, 31=fair)</li> <li>- Complete/partial pain relief was achieved in 85.6% of patients at 1 year. Complete pain relief in 64.9% at 6 mo, 70.3% (1 year), 75.4% (33 mo). Due to recurrence, only 55.8% of patients achieved complete/partial pain relief at 5 years</li> </ul> <p><b>3) Recurrent pain</b> Recurrence in 30 (13.6%) patients after initially achieving pain relief btw 2 -58 mo after GKS. Recurrences of pain occurred at a mean of 15.4 mo after therapy.</p> <p><b>4) Time to initial response (kaplan meier analysis)</b> Median time to achieving &gt;50% pain relief = 2 mo. Median time to achieving good/excellent pain relief=2mo.</p> <p><b>5) (multivariate analysis) Factors associated with time to response :</b> The rate of achieving &gt;=50% pain relief was faster in patients with typical TN vs with patients with atypical features (p=0.025). This factor is not significant with complete pain relief.</p> <p><b>6) Duration and maintenance of pain relief</b></p> <ul style="list-style-type: none"> <li>- A history of no previous surgery was the only factor significantly associated with achieving and maintaining complete pain relief (p=0.01).</li> <li>- The absence of pre-radiosurgery paraesthesias, which is strongly correlated with no prior surgery was significantly associated with achieving and maintaining &gt;50% pain relief.</li> </ul> <p><b>Correlation btw no. prior surgeries and preoperative paraesthesias</b></p> <table border="1" data-bbox="1211 1061 1601 1204"> <thead> <tr> <th rowspan="2">No. prior</th> <th colspan="2">Pre-op. paraesthesias</th> </tr> <tr> <th>No</th> <th>Yes</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>80</td> <td>5</td> </tr> <tr> <td>1</td> <td>45</td> <td>41</td> </tr> <tr> <td>2</td> <td>14</td> <td>25</td> </tr> <tr> <td>&gt;3</td> <td>1</td> <td>9</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>- 60/85 patients with no prior surgery maintained complete pain relief at 9 months and at 5 years vs. patients with prior surgery : 60% maintained complete pain relief at 1 year, 53% at 2 &amp; 33% at 5 years</li> </ul> <p><b>7) Complication/adverse effects</b></p> <ul style="list-style-type: none"> <li>- No early complication after a GKS procedure observed.</li> </ul>	No. prior	Pre-op. paraesthesias		No	Yes	0	80	5	1	45	41	2	14	25	>3	1	9	<p>patients with recurrent pain after MVD or percutaneous surgery has failed, even though previous surgical failure reduces radiosurgical success rate.</p> <p>GKS provides safe and effective management for patients with disabling, typical TN and these results were achieved in a patient population with a high frequency of prior surgical intervention.</p>
No. prior	Pre-op. paraesthesias																						
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					<p>- 17(7.7%) patients developed increased facial paraesthesias &amp;/or facial numbness (minor &amp; not bothersome) that lasted &gt; 6 mo.</p> <p>- 1 patient developed deafness after GKS (this patient had recurrent TN previously treated with MVD 8 yrs before this GKS, developed facial sensory loss &amp; some additional atypical pain features).</p> <p>facial paraesthesias &amp; numbness    17 patients deafness                                    1 patient mean time to develop paraesthesias    8 mo(1-19)</p> <p>- The median time to develop paraesthesias is 8 mo. After 19 months, no patient developed new sensory symptoms. Multivariate testing showed that the presence of a pre-radiosurgery sensory disturbance was important for developing an increased deficit following therapy (p=0.01).</p>																																													
Kondziolka et al., 1996 <sup>14</sup>	<p>Gamma knife surgery (GKS), Model B Leksell gamma knife, 50% isodose line, a single 4 mm collimator targeting at root entry zone</p> <p><b>D</b> = 60 to 90 Gy</p> <p><b>Design:</b> all centres applied similar techniques, case series, kaplan meier's product limit method, univariate and multivariate analysis</p>	<p>Multi-institutional centres-USA (Pittsburgh, Seattle, LA), France(Marseille), &amp; RI (Providence)</p> <p><b>In:</b> medically intractable typical TN</p> <p><b>Out :</b> -</p>	<p><b>TN type:</b> Idiopathic TN patients</p> <p><b>At beginning</b> <b>N</b> = 50 patients (32 had prior surgeries)</p> <p><b>At end</b> <b>N</b> = 50</p> <p><b>Age (mean/range) :</b> 70(40-87)</p> <p><b>M/F:</b> 20/30</p>	<p><b>Mean no. prior surgery before GKS :</b> 2.8/patient (1-7)</p> <p><b>FU:</b> patient self-assessment/coding of pain relief outcomes</p> <p><b>Mean FU (mo) =</b> 18 (11-36)</p> <p><b>Primary:</b>, facial pain outcomes - excellent (100% pain-free, no medication), good (50-90% improvement, reduced medication) &amp; poor (0%-50% improvement); latency interval to pain relief and repeated procedure. Improvement is defined as a reduction in both the frequency &amp; severity of TN attacks</p> <p><b>Adverse effects:</b> complications</p>	<p><b>1) Last FU, facial pain relief (med. time to response = 1 mo, range 1 day - 6.7mo)</b></p> <table border="1"> <thead> <tr> <th>Pain level</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>Excellent</td> <td>28(56%)</td> </tr> <tr> <td>Good</td> <td>16(32%)</td> </tr> <tr> <td>Poor</td> <td>6(12%)</td> </tr> </tbody> </table> <p>At 2 year, 94% achieved &gt;50% pain relief and 58% achieved complete pain relief. This could be due to excellent visualisation of the trigeminal nerve near the pons and radiobiological effect of irradiating the nerve in this location.</p> <p><b>2)Pain recurrence</b></p> <table border="1"> <thead> <tr> <th>Pain recurrence after initial good result</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>at 5 mo</td> <td>1</td> </tr> <tr> <td>at 7 mo</td> <td>1</td> </tr> <tr> <td>at 10 mo</td> <td>1</td> </tr> </tbody> </table> <p>All 3 patients had undergone additional surgery.</p> <p><b>3) Outcome after GKS (N=50), last FU, med=13 mo</b></p> <table border="1"> <thead> <tr> <th>Radiation dose</th> <th>Excellent</th> <th>Good</th> <th>Fair</th> </tr> </thead> <tbody> <tr> <td>60 Gy</td> <td>-</td> <td>6</td> <td>2</td> </tr> <tr> <td>65</td> <td>1</td> <td>1</td> <td>1</td> </tr> <tr> <td>70</td> <td>19</td> <td>6</td> <td>2</td> </tr> <tr> <td>75</td> <td>2</td> <td>-</td> <td>-</td> </tr> <tr> <td>80</td> <td>4</td> <td>2</td> <td>-</td> </tr> <tr> <td>90</td> <td>2</td> <td>1</td> <td>1</td> </tr> </tbody> </table> <p>The proportion of patients (28/39=72%) had complete</p>	Pain level	N	Excellent	28(56%)	Good	16(32%)	Poor	6(12%)	Pain recurrence after initial good result	N	at 5 mo	1	at 7 mo	1	at 10 mo	1	Radiation dose	Excellent	Good	Fair	60 Gy	-	6	2	65	1	1	1	70	19	6	2	75	2	-	-	80	4	2	-	90	2	1	1	<p>Study identified 3 important issues - target selection, patient selection &amp; dose range.</p> <p>A max dose of 70Gy was associated with greater pain relief than when lower doses (60Gy, 65Gy) were used. The irradiated target was the proximal nerve and REZ. The isocentre was positioned so that the brainstem surface was usually irradiated at no &gt; 20-30% of max isodose. It was hypothesised that a stronger radiobiological effect would occur at the proximal nerve where there was central oligodendrocyte myelin, which is sensitive to radiation Schwann cell myelin.</p> <p>Latency to pain relief was variable, from 1 to 8 wks.</p> <p>GKS should continue to be evaluated as part of the</p>
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					<p>pain relief was significantly &gt; in patients receiving <math>\geq 70\text{Gy}</math> (<math>p=0.0003</math>) vs. those (1/11=9%) receiving 60-65 Gy. The proportion of patients maintaining complete pain relief (last FU) was significantly &gt; (<math>p=0.0009</math>) when a dose of <math>\geq 70\text{Gy}</math> was delivered.</p> <p><b>4) Prior vs. none prior surgery</b> Patients without prior surgery had better outcomes than those with prior surgery (<math>p=0.14</math>), although not statistically significant.</p> <p>Multivariate analysis :</p> <ul style="list-style-type: none"> <li>of the complete response rate identified dose as the only significant factor (<math>p=0.016</math>)</li> <li>types of prior TN surgery did not affect outcome</li> </ul> <p><b>5) MS-related TN</b> 2 multiple sclerosis patients with TN responded to GKS with 70Gy.</p> <p><b>6) Complication/adverse effects</b> No other neurological or systemic morbidity caused by GKS treatment. Only complication is increased facial paraesthesias and decreased sensation after GKS at 65GY, 70Gy and 75Gy. These symptoms resolved completely after 6 wks and in another sub-total improvement occurred.</p> <p><b>7) dose-response relationship in trigeminal nerve irradiation.</b> In Pittsburgh, 5 consecutive patients were given radiation therapy starting with 60Gy. A significant difference in pain control in patients with max. <math>\geq 70\text{Gy}</math> (<math>p=0.03</math>) for good/excellent pain relief and <math>p=0.02</math> for pain-free result. Higher doses (max 90Gy) have not led to improvement.</p>	<p>surgical approach to the management of recurrent TN or as a primary procedure for elderly or medically infirm patients.</p> <p>Long-term FU on higher dose data analysis is undergoing.</p>														
Kondziolka et al., 1997 <sup>15</sup>	Gamma knife surgery (GKS), Leksell gamma knife, a single 4mm collimator targeting at mid-portion of the trigeminal nerve $\approx 2$ to 4 mm anterior to the	University of Pittsburgh  <b>In:</b> typical medically intractable idiopathic TN, patients with single-session of GKS only.	<b>TN type:</b> typical TN patients  <b>At beginning</b> <b>N</b> = 80 patients (4 are multiple sclerosis patients)  <b>Age:</b> <b>(mean/range)</b>	<b>No. prior surgery before GKS (mean):</b> 3 (1-8) 65 (81%) patients had prior surgery.  <b>FU:</b> patients are told to expect a period of latency of up to 10 wks. Once pain relief has been obtained $\geq 3 - 4$ days, medication was	<p><b>1) Facial pain relief</b></p> <table border="0"> <tr> <td><u>Dosage</u></td> <td><u>No. patients sustained pain relief</u></td> </tr> <tr> <td><u>Initial response</u></td> <td></td> </tr> <tr> <td>60-65Gy</td> <td>5 out of 6</td> </tr> <tr> <td>70-90Gy</td> <td>61 out of 66 (92%)</td> </tr> <tr> <td></td> <td>(37=pain free &amp; 24=significant improvement)</td> </tr> <tr> <td><u>Mean FU=18mo</u></td> <td>7 (good result)</td> </tr> <tr> <td></td> <td>(developed recurrence)</td> </tr> </table> <p>With longer FU, 37=pain free &amp; 17= improvement. All</p>	<u>Dosage</u>	<u>No. patients sustained pain relief</u>	<u>Initial response</u>		60-65Gy	5 out of 6	70-90Gy	61 out of 66 (92%)		(37=pain free & 24=significant improvement)	<u>Mean FU=18mo</u>	7 (good result)		(developed recurrence)	<p>Patients initially selected only if they failed prior surgery.</p> <p>Authors did not analyse data on MS-TN</p> <p>GKS is effective and safe.</p> <p>GKS is an important primary</p>
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	(developed recurrence)																			

	<p>junction of the nerve and brain stem. Brainstem receives &lt;20% isodose, length of nerve irradiated at 50% is 4mm</p> <p><b>D = 70Gy</b> (patients with no prior surgery), 80Gy (recurrent TN), 85 Gy &amp; 90 Gy</p> <p><b>Design:</b> case series</p>	<p><b>Out:</b> patients with constant facial pain, Tumour-or vascular malformations</p>	<p><b>D:</b> 65(21-91)</p> <p><b>M/F:</b> <b>D:</b> 34/46</p>	<p>tapered.</p> <p><b>Mean FU (mo) = 18</b></p> <p><b>Primary:</b> pain relief at initial and mean FU.</p> <p><b>Adverse effects:</b> complications</p>	<p>patients who had initially had excellent results maintained those results throughout FU.</p> <p><b>2) without prior vs. with prior surgeries</b> Initial response, patients with prior surgery, 24 patients became pain free, 18 had significant improvement, 4 did not respond to GKS. Mean FU (18mo), 24 remained pain free, 12 had improved pain relief and 10 had little to no pain relief</p> <p><b>3) repeated GKS = none</b></p> <p><b>4) Complication/adverse effects</b> No other complications apart from increased paraesthesias. 2/76 evaluable patients (2.6%) noted increased paraesthesias but not bothersome.</p>	<p>management strategy for TN and for patients in whom prior surgeries have been unsuccessful.</p>
Kondziolka et al., 1998a <sup>16</sup>	<p>Gamma knife surgery (GKS), Leksell gamma knife, a single 4mm collimator targeting at proximal trigeminal nerve</p> <p><b>D = 70Gy</b> (14 patients), 80Gy (9 patients)</p> <p><b>Design:</b> case series</p>	<p>University of Pittsburgh, 1993-1996</p> <p><b>In:</b> GKS as first surgery, patients with medical contraindications to open surgery</p> <p><b>Out:</b> patients with prior surgery before GKS</p>	<p><b>TN type:</b> typical TN patients</p> <p><b>At beginning</b> <b>N = 23 patients</b></p> <p><b>Age:</b> <b>(mean/range)</b> <b>D:</b> 66(48-91)</p> <p><b>M/F:</b> <b>D:</b> 34/46</p>	<p><b>FU:</b> patients are told to expect a period of latency of up to 10 wks. Once pain relief has been obtained &gt;= 3 - 4 days, medication was tapered.</p> <p><b>Mean FU (mo) = 12 (5-33)</b></p> <p><b>Primary:</b> pain relief - poor (0-50% improvement); good (50%-90% improvement) &amp; excellent (100% pain free, off medications). Criteria for improvement included a reduction in both the frequency &amp; severity of pain attacks</p> <p><b>Adverse effects:</b> complications</p>	<p><b>1) Facial pain relief</b> Pain level                      N (%) (dosage) _____ Excellent                      17(74%) (9 received 70Gy &amp; 8 (80Gy)) Good                              5(22%) (4 received 70Gy &amp; 1 (80%)) Poor                                1(4%) (70Gy &amp; subsequently had MVD)</p> <p>The latency period for pain varied from 1 - 12 wks.</p> <p><b>2) Morbidity</b> No patient developed facial numbness/sensory loss. No complication.</p>	<p>GKS is the least invasive procedure for TN and is an effective biologic treatment for TN.</p> <p>Early results are encouraging with acceptable rates of pain control.</p> <p>Long term results required.</p>
Kondziolka et al., 1998b <sup>17</sup>	<p>Gamma knife surgery (GKS), Leksell gamma knife (Model B &amp; U) a single 4mm isocentre targeting at proximal</p>	<p>University of Pittsburgh,</p> <p><b>In:</b> idiopathic TN &amp; multiple sclerosis (MS)</p> <p><b>Out:</b> Tumour related TN</p>	<p><b>TN type:</b> typical TN patients</p> <p><b>At beginning</b> <b>N = 121 patients</b> (11 MS-TN patients) <b>At end :</b> n=106</p>	<p><b>Mean duration of pain= 11 mo</b></p> <p><b>No. patients had prior surgery before GKS : 118 patients</b> 22% patients had no prior surgery.</p>	<p><b>1) Facial pain relief, median time to response = 4 wks (1 day - 3 mo)</b> Pain level                      N (%) Excellent                      64(60) Good                              18(17) Poor                                24(23)</p> <p>Initial improvement noted in 91 patients (86%). At last FU, significant pain relief (good &amp; excellent) noted in 77%</p>	<p>Study aimed to identify an appropriate radiation dose that might eliminate pain more rapidly and still maintain facial sensation.</p> <p>GKS is the least invasive surgical procedure for TN</p>

	<p>trigeminal nerve anterior to the pons.</p> <p><b>D</b> = 70Gy (54 patients with no prior surgery) &amp; 80Gy for patients with recurrent TN after prior surgery(60 patients), 85Gy (5) &amp; 90Gy(2)</p> <p><b>Design:</b> case series, single blinded assessor, univariate &amp; multivariate tests</p>		<p><b>Age:</b> <b>(mean/range)</b> <b>D:</b> 67(32-92)</p> <p><b>M/F:</b> <b>D:</b>na</p>	<p>38% had facial numbness</p> <p><b>FU:</b> physician blinded to study, patients' own descriptions of clinical status.</p> <p><b>Mean FU (mo)</b> = 18 (6-48)</p> <p><b>Primary:</b> pain relief - poor/failure (no pain relief or &lt;10% relief), fair (10%-50%), good response (50-90% relief but still on medications if used pre-op), excellent (100% pain free, no medication). Criteria for improvement included a reduction in both the frequency &amp; severity of pain attacks</p> <p><b>Adverse effects:</b> rates of morbidity, complications</p>	<p>patients. Recurrence noted in only 6 (10%) of 64 patients who attained complete relief from 2 to 10 mo fr. onset of complete relief.</p> <p><b>2) Pain response and radiosurgery dose</b> No significant difference in pain relief at 70Gy (p=0.57) vs. 80-90Gy for complete relief &amp; good+excellent results (p=037)</p> <p><b>Multivariate study - No significant difference between pain relief and other factors</b> s.a age, history of prior surgery, history of facial numbness, gamma knife model, and surgeon's ability.</p> <p><b>4) Complication/adverse effects</b> 12 patients (10%)developed new/increased paraesthesias/ sensory loss/numbness.</p> <p>Age, MS, sex, radiation dose, gamma knife model, or nerve identification did not correlate with the onset of sensory findings (p&gt;0.05).</p> <p>There was a trend of a lower rate of sensory findings in patients with no prior surgery (p=0.08)</p> <p>No other complications (or anaesthesia dolorosa/constant deafferentation pain)</p>	<p>with no systemic morbidity found.</p>														
Kondziolka et al., 2002 <sup>18</sup>	<p>Gamma knife surgery (GKS), Leksell gamma knife Model A &amp; B, a single 4mm isocentre targeting ≈ 2 to 4 mm anterior fr. the junction of the nerve &amp; pons/brain stem.</p> <p><b>D</b> = 60 to 90 Gy (patients evaluated at 5 year received only 60=65 Gy)</p> <p><b>Design:</b> case series, single-</p>	<p>University of Pittsburgh</p> <p><b>In:</b> idiopathic TN, long standing, refractory to medication therapy</p> <p><b>Out:</b> Tumour-related, MS-related, other pathological conditions (herpetic infection, Lyme disease, wallenberg syndrome)</p>	<p><b>TN type:</b> typical and atypical TN patients</p> <p><b>At beginning</b> <b>N</b> = 220</p> <p><b>At end, n=</b> 173 (47 patients excluded fr. analysis as they required repeated GKS)</p> <p><b>Age:</b> <b>(mean/range)</b> <b>D:</b> 70(26-92)</p> <p><b>M/F:</b> <b>D:</b> 94/126</p>	<p><b>Mean pain duration=</b> 96mo(3-564). Pre-op, 80 (36.4%) patients had some sensory disturbance (usually paraesthesias). 3 patients had partial deafferentation pain due to prior ablative procedures.</p> <p><b>No. patients with prior surgery before GKS:</b> 135(61.4%).</p> <p><b>FU:</b> patients' self-assessed with blinded assessor via telephone.</p> <p><b>Mean FU (mo)</b> = 22(6-78)</p>	<p><b>1) Facial pain relief, mean time response to GKS=2mo.</b> (most patients responded within 6 mo)</p> <table border="1"> <thead> <tr> <th>Pain level</th> <th>N (%)</th> </tr> </thead> <tbody> <tr> <td>Excellent</td> <td>105(47.7%)</td> </tr> <tr> <td>Good</td> <td>34</td> </tr> <tr> <td>Fair</td> <td>42</td> </tr> </tbody> </table> <p><b>Initial FU</b> within 6mo of GKS :</p> <p>- 47.7% patients achieved excellent results, 63.2% had excellent plus good results. 82.3% achieved &gt;50% pain relief.</p> <p>- No prior vs. prior surgery = 68% (6 mo) &amp; 76% (1 year) vs. 63% (6 mo) &amp; 70% (1year) for achievement of pain relief - no significant difference between the 2 groups.</p> <p><b>Last FU :</b></p> <table border="1"> <tbody> <tr> <td>Excellent</td> <td>88(40%)</td> </tr> <tr> <td>Good</td> <td>63</td> </tr> <tr> <td>Fair</td> <td>31</td> </tr> </tbody> </table> <p>40% patients achieved excellent results at last FU evaluation.,55.9% had excellent plus good results while 69.1% achieved &gt;50%.</p>	Pain level	N (%)	Excellent	105(47.7%)	Good	34	Fair	42	Excellent	88(40%)	Good	63	Fair	31	<p>Interesting finding of 10% patients who achieved partial relief within 6 mo but went on to a complete resolution of pain afterwards (6-33mo).</p> <p>Patients with atypical features has a poor response to radiosurgery. Such features are constant dull, burning pain, tingling sensation + typical TN features. Generally they tend to be refractory to any other surgical methods. Because atypical features may be related to varying degrees of underlying nerve injury, a procedure that causes additional axonal effects may</p>
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	blind (assessor), kaplan-meier analysis			<p><b>Primary:</b> pain relief - poor/failure (no pain relief or &lt;10% relief), fair (10%-50%), good response (50-90% relief but still on medications if used pre-op), excellent (100% pain free, no medication). Criteria for improvement included a reduction in both the frequency &amp; severity of pain attacks.</p> <p><b>Adverse effects:</b> complications</p>	<p><b>2) Time to initial response (Kaplan meier)</b></p> <ul style="list-style-type: none"> <li>- Mean time to initial response from achieving &gt;50% pain relief (excellent, good &amp; fair) &amp; complete pain relief (excellent+good) = 2 mo (2.0±0.05) &amp; 2 mo (2.0±5.1), respectively.</li> <li>- At 6mo &amp; at 12mo, 81.4(±2.6)% &amp; 85.6(±2.47)% patients respectively achieved &gt;50% relief.</li> <li>- At 6mo &amp; at 12mo, 64.9(±3.2)% &amp; 70.3(±3.16)% patients respectively achieved complete relief (excellent&amp; good) and by 33 mo, 75.4(±3.16)%.</li> <li>- Multivariate analysis suggested the rate of relief for patients with typical TN faster vs. patients with additional atypical pain. No significant difference was found in this factor.</li> </ul> <p><b>3) Recurrence</b></p> <p>30 patients (13.6%) had recurrent pain after initial achievement (25 after complete relief &amp; 5 after partial or &gt;50% relief). Recurrences occurred at medium = 15.4 mo (2-58) after GKS.</p> <p><b>4) Latency/Achievement of pain relief</b> (actuarial statistics)</p> <ul style="list-style-type: none"> <li>- 81.4(±2.6)% patients responded to treatment within 6 mo (med=2mo) &amp; complete pain relief achieved in 2mo for most patients.</li> <li>-15% patients had no relief even after 12 mo.</li> <li>- A further 10% achieved pain relief 6 to 33 mo after GKS. All these patients achieved partial relief within 6 mo but full relief afterwards.</li> <li>- Atypical TN has a poor response to GKS vs. typical TN. 43.8(±12.4)% atypical TN patients vs 84.4(±2.6)% TN patients achieved pain relief at 6mo.</li> </ul> <p><b>5)Maintenance of pain relief</b> (kaplan meier's product limit)</p> <table border="1" data-bbox="1211 1169 1720 1329"> <thead> <tr> <th>&gt;50% pain relief(excellent,good&amp;fair)</th> <th>% patients</th> </tr> </thead> <tbody> <tr> <td>Year 1</td> <td>75.8±2.9</td> </tr> <tr> <td>Year 2</td> <td>71.3±3.3</td> </tr> <tr> <td>Year 3</td> <td>67.2±3.9</td> </tr> <tr> <td>Year 3.5</td> <td>65.1±4.3</td> </tr> <tr> <td>Year 5</td> <td>55.8±9.3</td> </tr> </tbody> </table> <p><b>Complete pain relief(excellent/good) achieved &amp; maintained at :</b></p>	>50% pain relief(excellent,good&fair)	% patients	Year 1	75.8±2.9	Year 2	71.3±3.3	Year 3	67.2±3.9	Year 3.5	65.1±4.3	Year 5	55.8±9.3	<p>provide no benefit.</p> <p>Preoperative paraesthesias and prior surgery were factors associated with duration of pain relief. Prior surgery may have injured the trigeminal nerve and caused a sensory disturbance.</p> <p>Primary radiosurgery could provide a high rate of pain control (as is found in MVD).</p> <p>Effects of radiosurgery likely to be a combination of both histologic and electrophysiologic responses.</p>
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					<p>Year 1 63.6±3.3  Year 2 59.2±3.5  Year 3 56.6±3.8  Year 5 37.7±15.6 (this result was achieved with patients receiving lower radiation dose of 60-65Gy)</p> <p><b>6) No prior surgery history - duration of pain relief</b>  - A history of no prior surgery is the only significant factor to achieve and maintain complete pain relief (p=0.01)  - The absence of presurgery paraesthesias (which is strongly correlated with no-prior-surgery) was significantly associated with achieving and maintaining &gt; 50% relief (p=0.024).  - 70% (85) patients without prior surgery maintained complete pain relief at 9 mo and also at 5 years. No recurrence observed in this group past 9 mo. Vs. 60% (1 year), 53% (2 year) &amp; 33% (5 year)</p> <p><b>7) Radiosurgical morbidity</b>  - Minor increased paraesthesias and/or facial numbness = 17 patients  - deafferentation pain = 1 patient who had recurrent TN after MVD</p>																																							
Flickinger et al, 2001 <sup>19</sup>	<p>Gamma knife surgery (GKS), 4mm collimator</p> <p><b>D=</b> 75 Gy  <b>C1=</b> 1 isocentre  <b>C2=</b> 2 isocentres 3 - 5 mm apart  (1 isocentre was always placed close to the root-entry zone of the nerve, with 50% isodose vol. always outside the brainstem. Mean trigeminal nerve length=5.4±0.4 mm for C1 &amp; 8.7±1.1 mm for C2</p>	<p>Mayo clinic, Rochester &amp; University of Pittsburgh</p> <p><b>In:</b> typical TN  <b>Out:</b> tumour-, MS- related and patients with only atypical pain features.</p> <p><b>Power of calculation =</b> 80% (p=0.05)</p>	<p><b>TN type:</b>  Idiopathic TN patients</p> <p><b>At beginning</b>  <b>N =</b> 88 patients  <b>C1=</b> 44  <b>C2=</b> 44</p> <p><b>At end</b>  <b>N =</b> 87</p> <p><b>Age:</b>  <b>(mean/range)</b>  <b>C1:</b> 68(37-86)  <b>C2:</b> 69(38-90)</p> <p><b>M/F:</b>  <b>C1:</b> 19/24  <b>C2:</b> 18/26</p>	<p><b>Pain duration (yr):</b>  <b>C1 =</b> 7(1-31)  <b>C2 =</b> 9(0.6-55)</p> <p><b>No. prior surgery before GKS (no.):</b></p> <table border="1"> <thead> <tr> <th>No. procedures</th> <th>C1</th> <th>C2</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>12</td> <td>12</td> </tr> <tr> <td>1</td> <td>9</td> <td>14</td> </tr> <tr> <td>2</td> <td>9</td> <td>9</td> </tr> <tr> <td>3-7</td> <td>14</td> <td>8</td> </tr> <tr> <td>Total patients</td> <td>43</td> <td>44</td> </tr> </tbody> </table> <p><b>Prior numbness :</b>  <b>C1=</b> 20 patients  <b>C2=</b> 17 patients</p> <p><b>Prior procedures= C1vsC2</b>  <b>0 =</b> 12 vs 12 patients  <b>1 =</b> 9 vs 14 patients  <b>2 =</b> 9 vs 9 patients  <b>3 - 7 =</b> 14 vs 8 patients</p> <p><b>Mean FU (mo) =</b> 26 (1-36)</p>	No. procedures	C1	C2	0	12	12	1	9	14	2	9	9	3-7	14	8	Total patients	43	44	<p><b>1) Initial facial pain outcomes</b>  - Complete pain relief in 57 patients (12 still used low dose medication &amp; 45 none) in mean time of 3 mo (1wk - 17mo) after GKS.  - Partial relief in 15 patients  - No benefit in 15 patients  Actuarial rate of obtaining complete relief (with/without medication) = 67.7±5.1%  <u>Max. pain control after GKS</u></p> <table border="1"> <thead> <tr> <th>pain response</th> <th>C1(n=44)</th> <th>C2(n=43)</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>no pain, no drugs</td> <td>24</td> <td>21</td> <td>45</td> </tr> <tr> <td>no pain with drugs</td> <td>5</td> <td>7</td> <td>12</td> </tr> <tr> <td>decreased with drugs</td> <td>8</td> <td>7</td> <td>15</td> </tr> <tr> <td>no response</td> <td>7</td> <td>8</td> <td>15</td> </tr> </tbody> </table> <p>- The proportions achieving diff. categories of pain relief were essentially identical for C1=C2</p> <p><u>Pain Recurrence</u>  - 30 out of 72 patients responded to GKS with a med = 12 mo (2-31) after pain relief.  - 14 of 45 patients with complete relief without medication.  - 9 of 12 with complete relief but on low dose of drugs.  - 7 of 15 patients with partial relief.</p>	pain response	C1(n=44)	C2(n=43)	Total	no pain, no drugs	24	21	45	no pain with drugs	5	7	12	decreased with drugs	8	7	15	no response	7	8	15	<p>Study examining nerve length in relation to pain relief.</p> <p>Irradiating a longer nerve length with second isocentre did not improve the pain control appreciably but did increase the complications (new/increased post-radiosurgery numbness/paraesthesias.</p> <p>Pain relief correlated with age and no prior surgeries.</p>
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<p><b>Design:</b> double-blind, randomised, kaplan-meier, multivariate, univariate studies</p>			<p><b>Primary:</b> facial pain outcomes <b>Adverse effects:</b> complication</p>	<p>Relapse was &lt; in C2 vs. C1 but not statistically significant (p=0.45).</p> <p><b>2) At last FU</b> <u>Pain control after GKS</u></p> <table border="1"> <thead> <tr> <th>pain response</th> <th>C1(n=44)</th> <th>C2(n=43)</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>no pain, no drugs</td> <td>15</td> <td>18</td> <td>33</td> </tr> <tr> <td>no pain with drugs</td> <td>5</td> <td>5</td> <td>10</td> </tr> <tr> <td>decreased with drugs</td> <td>12</td> <td>10</td> <td>22</td> </tr> <tr> <td>no response</td> <td>12</td> <td>10</td> <td>22</td> </tr> </tbody> </table> <p>The proportions achieving diff. categories of pain relief were essentially still identical for C1=C2</p> <p><b>3) Additional surgery after GKS</b> 22 patients had repeated surgery afterward.</p> <table border="1"> <thead> <tr> <th>Additional surgery</th> <th>No. patients</th> </tr> </thead> <tbody> <tr> <td>glycerol rhizotomy</td> <td>7</td> </tr> <tr> <td>repeated GKS</td> <td>9</td> </tr> <tr> <td>mvd</td> <td>3</td> </tr> <tr> <td>radiofrequency rhizotomy</td> <td>1</td> </tr> <tr> <td>peripheral alcohol blocks</td> <td>2</td> </tr> </tbody> </table> <p><b>4) Complication/adverse effects</b> 21 patients developed new/increased trigeminal dysfunction (numbness/paraesthesias) and had been persistent to date. No significant trend found between C1 &amp; C2 on complications. 37 vs. 29 for C1 vs. C2 had no new problems.</p> <table border="1"> <thead> <tr> <th>Complications</th> <th>C1</th> <th>C2</th> </tr> </thead> <tbody> <tr> <td>numbness</td> <td>3</td> <td>8</td> </tr> <tr> <td>mild paraesthesias</td> <td>4</td> <td>5</td> </tr> <tr> <td>severe paraesthesias</td> <td>0</td> <td>1</td> </tr> </tbody> </table> <p>2-yr actuarial rate for new/increased trigeminal nerve deficits 32.5±7.5% 16.8±5.8%</p> <p>(p=0.11)</p> <p><b>5) Multivariate analysis</b> - Decreased pain relief correlated with age (p=0.025) &amp; no. prior procedures (p=0.039). The actuarial data for achieving complete pain relief = 71.4±6.6% for patients aged &lt; 70 vs. 63.2±7.9% for patients ≥70. The actuarial data for achieving complete pain relief = 75±8.8% for patients without prior surgeries vs.</p>	pain response	C1(n=44)	C2(n=43)	Total	no pain, no drugs	15	18	33	no pain with drugs	5	5	10	decreased with drugs	12	10	22	no response	12	10	22	Additional surgery	No. patients	glycerol rhizotomy	7	repeated GKS	9	mvd	3	radiofrequency rhizotomy	1	peripheral alcohol blocks	2	Complications	C1	C2	numbness	3	8	mild paraesthesias	4	5	severe paraesthesias	0	1
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					69.6±9.6% with 1 prior surgery, & 62.5±8% for patients with >= 2 prior surgeries.  - An increased in complications correlated with an increase in nerve length irradiated (p=0.018, hazard rate ratio=1.36, 95%CI 1.06-1.76). Other factors were not significant.																																									
Zheng et al., 2001 <sup>20</sup>	Gamma knife surgery (GKS), Leksell gamma knife, Model B, a single isocentre - 4mm collimator positioned at the trigeminal nerve entry zone, 4-6mm fr. the brainstem surface - no > than 20% isodose administered to brainstem)  <b>D : mean (range) = 75.6(70- 90Gy)</b>  <b>Design:</b> case series	Tianjin Medical University, China, Nov. 1996-Apr. 1999  <b>In:</b> medically refractory, primary TN,  <b>Out:</b> patients with tumour	<b>TN type:</b> primary TN patients  <b>At beginning</b> <b>N = 80 patients</b>  <b>Age:</b> <b>mean(range)</b> : 67(32-92)  <b>M/F:</b> 31/49	<b>Pain duration(yr) :</b> 7.6(1.5-29)  <b>FU:</b> telephone records, questionnaire  <b>Mean FU (mo) =</b> 23.7 (12-43)  <b>Primary:</b> pain relief - no response (0-50% improvement); effective response (50-80% improvement with medication), good response (80-100% improvement, off medications) & excellent response (100% pain free, no medication).  <b>Adverse effects:</b> complications	<b>1) Facial pain relief</b> <table border="1"><thead><tr><th>Pain level</th><th>N (%)</th></tr></thead><tbody><tr><td>Excellent response</td><td>42(52.5%)</td></tr><tr><td>Good response</td><td>25(31.25%)</td></tr><tr><td>Effective response</td><td>8(10%)</td></tr><tr><td>No response</td><td>5(6.25%)</td></tr></tbody></table> - The latency period for pain = 1 day - 17 wks (mean 22 days). - Initial pain control = 93.75%  <b>2) Recurrence</b> - 7 of 75 patients with pain relief (excellent, good & effective) had recurrent 5 -26 mo after being completely pain free. - Distribution and severity of pain before = after GKS. -2nd GKS on all 7 patients (mean max=74.2Gy), 5 had treatment failure.  <b>3) At mean FU = 18 mo (8-33)</b> Excellent response = 9 patients Good response = 2 patients -Latency period = 1 day - 17 wks (mean= 15 days)  <b>3) Complications</b> At last FU, 9 patients developed new facial numbness. No other complications or morbidity observed.	Pain level	N (%)	Excellent response	42(52.5%)	Good response	25(31.25%)	Effective response	8(10%)	No response	5(6.25%)	GKS is a safe and effective method in the treatment of TN once diagnosis is established.																														
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Effective response	8(10%)																																													
No response	5(6.25%)																																													
Urgosik et al, 1998 <sup>21</sup>	Gamma knife surgery (GKS), a single 4mm collimator, targeting at the root close to brainstem. Dose to brainstem = 8 to16Gy (mean=13)	Czech Republic, Oct 1995-Oct 1996  <b>In:</b> mostly patients who had prior surgery.  <b>Out:</b> tumour-related	<b>TN type:</b> Idiopathic TN patients: 31=essential TN (EN), 7=MS-TN (MS), 3=atypical TN (AN), 8=postherpetic neuralgia(PN)  <b>At beginning</b>	<b>No. prior surgery before GKS (no.):</b> <table border="1"><thead><tr><th>Patients</th><th>Prior Surgery</th></tr></thead><tbody><tr><td>EN (31)</td><td>27(87%)</td></tr><tr><td>MS (7)</td><td>5(71%)</td></tr><tr><td>AN (3)</td><td>3(100%)</td></tr><tr><td>PN (8)</td><td>2(25%)</td></tr></tbody></table> Mean = 2.4 (1-8) 13 patients had no prior surgery.	Patients	Prior Surgery	EN (31)	27(87%)	MS (7)	5(71%)	AN (3)	3(100%)	PN (8)	2(25%)	<b>1) facial pain outcomes</b> The success rate (excellent, very good & good in pain relief) was 77%. <table border="1"><thead><tr><th>TN type</th><th>I</th><th>II</th><th>III</th><th>IV</th><th>V</th></tr></thead><tbody><tr><td>EN</td><td>21(68%)</td><td>1(3%)</td><td>2(%)</td><td>-</td><td>7(23%)</td></tr><tr><td>MS</td><td>3(42.8%)</td><td>-</td><td>1(14.3%)</td><td>1(14.3%)</td><td>2(28.6%)</td></tr><tr><td>AN</td><td>1(33.3%)</td><td>-</td><td>-</td><td>-</td><td>2(66.6%)</td></tr><tr><td>PN</td><td>3(37.5%)</td><td>-</td><td>-</td><td>1(12.5%)</td><td>4(50%)</td></tr></tbody></table>	TN type	I	II	III	IV	V	EN	21(68%)	1(3%)	2(%)	-	7(23%)	MS	3(42.8%)	-	1(14.3%)	1(14.3%)	2(28.6%)	AN	1(33.3%)	-	-	-	2(66.6%)	PN	3(37.5%)	-	-	1(12.5%)	4(50%)	Clinical & electrophysiological study.  Data for AN insufficient for meaningful analysis.  PN is also refractory to surgery, apart fr. drugs.  Authors did not analyse results of patients with vs.
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	<p><b>D=</b> 70 Gy(25 cases) and 80 Gy(24 cases)</p> <p><b>Design:</b> case series</p>		<p><b>N</b> = 49 patients</p> <p><b>Age:</b> <b>(mean/range)</b> 68(38-94)</p> <p><b>M/F:</b> 23/26</p>	<p><b>Baseline period :</b> Before irradiation, all patients were examined neurologically, &amp; 18 also underwent electrophysiological control.</p> <p><b>FU:</b> All patients clinically examined 1 mo after GKS and every 6 mo thereafter. The 18-electrophysiological-control patients underwent repeated electrophysiological control (EMG) as well. 16 of them also underwent detailed sensation examination. All patients had MRI control 6 and 12 mo after GKS. Patients self-assessed pain relief using the percentile scale.</p> <p><b>Mean FU (mo) =</b> 13 (10-19)</p> <p><b>Primary:</b> (1) electrophysiological control via electromyography (EMG) of the masseter muscle &amp; Blink reflex (BR) (2) examination of sensation (tactile, algescic &amp; thermal), (3) clinical factors.</p> <p>Pain relief defined as residual pain - group I/excellent (0-20%), group II/very good(21-40%), group III/good (41-60%), group IV/poor (61-80%) &amp; group V/very poor (81-100%)</p> <p><b>Adverse effects:</b> complications</p>	<p>- Of the 21 EN patients, 20 achieved complete pain relief or 65% (20/31). - Pain relief better in EN &gt; MS-related TN.</p> <p><b>2) Recurrence of pain</b></p> <table border="1" data-bbox="1211 316 1720 443"> <thead> <tr> <th>TN type</th> <th>No.recurrences</th> <th>Time interval(mo)</th> </tr> </thead> <tbody> <tr> <td>EN</td> <td>4(13%)</td> <td>1-15</td> </tr> <tr> <td>MS</td> <td>3(43%)</td> <td>4-9</td> </tr> <tr> <td>AN</td> <td>1(33.3%)</td> <td>14</td> </tr> <tr> <td>PN</td> <td>1(12.5%)</td> <td>9</td> </tr> </tbody> </table> <p>- Only patients who had prior surgeries had pain recurrence. - Recurrence of pain in EN was 13%, explained by high rate of prior surgeries (87%). - Recurrence of pain was also &gt; in MS patients than EN patients.</p> <p><b>3) Complication/adverse effects</b></p> <p>- No signs of motor impairment observed - normal tone in masticatory muscles, without chewing problems during eating. - Tactile hypaesthesia found in 3 patients who were unaware of it. - 5 of 16 patients examined in detailed before GKS, had some impairment in either thermal or algescic sensation almost exclusively in the distribution of the pain. - No new deafferentation pain registered after GKS - EMG examination found slight signs of denervation in 2 of the 18 patients investigated before GKS. - No changes of blink reflex after GKS.</p>	TN type	No.recurrences	Time interval(mo)	EN	4(13%)	1-15	MS	3(43%)	4-9	AN	1(33.3%)	14	PN	1(12.5%)	9	<p>without prior surgery.</p> <p>GKS more effective with EN than MS-TN.</p> <p>GKS is an effective and safe method of treatment.</p>
TN type	No.recurrences	Time interval(mo)																			
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Brisman & Mooij,	Gamma knife surgery (GKS) B, a single 4mm	New York, May 1998-Feb2000	<b>TN type:</b> Idiopathic TN	<b>FU:</b> either by mail or phone interview, a standardised	<b>1) facial pain outcomes</b>  <b>At 6 mo after GKS ::</b>	Study examined volume of brainstem vs. clinical outcomes.															

2000 <sup>22</sup>	<p>collimator, targeting at the nerve root close to brainstem.</p> <p><b>Max D=</b> 75 Gy</p> <p>Study assessing <u>2 factors</u> in relation to outcome, i.e. (1) <b>VB20</b> = volume of the brainstem that receives <math>\geq 20\%</math> of the max. dose (2) <b>VT50</b> = volume of the trigeminal nerve that receives <math>\geq 50\%</math> of the max dose</p> <p><b>Design:</b> case series</p>	<p><b>In:</b> patients with TN, not adequately controlled with drugs</p> <p><b>Out:</b> -</p>	<p>patients:</p> <p><b>At beginning</b> <b>N</b> = 126 patients</p> <p><b>Age:</b> <b>(mean/range)</b> -</p> <p><b>M/F:</b> -</p>	<p>questionnaire administered at 6mo in 126 patients &amp; 12mo in 84 patients,</p> <p><b>Mean FU (mo) = -</b></p> <p><b>Primary: VB20 &amp; VT50</b> correlated with pain response defined as excellent (no pain, no drug), good (<math>\geq 50\%</math> improvement, occasional pain &amp; no drug or 50-100% pain relief &amp; drug that didn't induce discomfort); laterality, presence of multiple sclerosis (MS) &amp; each other</p> <p><b>Adverse effects:</b> complications</p>	<table border="1" data-bbox="1070 201 1601 320"> <thead> <tr> <th>MS</th> <th>Excellent</th> <th>VB20&lt;20mm<sup>3</sup>(n)</th> <th>VB20≥20mm<sup>3</sup>(n)</th> <th>Σ</th> </tr> </thead> <tbody> <tr> <td>no</td> <td>yes</td> <td>22(36.7%)</td> <td>25(55.6%)</td> <td>47</td> </tr> <tr> <td>no</td> <td>no</td> <td>38(63.3%)</td> <td>20(44.4%)</td> <td>58</td> </tr> <tr> <td>yes</td> <td>yes</td> <td>3</td> <td>2</td> <td>5</td> </tr> <tr> <td>yes</td> <td>no</td> <td>15</td> <td>1</td> <td>16</td> </tr> </tbody> </table> <p>- Excellent results significantly <math>&gt;</math> likely when <math>VB20 \geq 20mm^3</math> (<math>p=0.035</math>). This is not affected by patient age (<math>p=0.306</math>), laterality (<math>p=0.481</math>), sex (<math>p=0.477</math>), history of TN surgery (<math>p=0.645</math>), interval fr. 1st symptom to GKS (<math>p=0.323</math>), VT50 (<math>p=0.415</math>) or absence of MS (<math>p=0.149</math>).</p> <p>- Absence of MS was significant after <math>VB20 \geq 20mm^3</math> was taken out.</p> <p>- Excellent pain relief for 27/48 (56%) when <math>VB20 \geq 20mm^3</math> &amp; for 25/78 (32%) when <math>VB20 &lt; 20mm^3</math> (<math>p=0.009</math>).</p> <p>- Excellent pain relief was <math>&gt;</math> likely for TN without MS as <math>VB20 \uparrow</math> (<math>p=0.049</math>) when dependent variables = age, laterality, sex, history of TN surgery, interval fr. 1st symptom, &amp; all <math>VB20</math> numbers, and <math>p=0.086</math> when VT50 was included.</p> <p><b>At 12 mo after GKS:</b></p> <table border="1" data-bbox="1070 651 1601 770"> <thead> <tr> <th>MS</th> <th>Excellent</th> <th>VB20&lt;20mm<sup>3</sup>(n)</th> <th>VB20≥20mm<sup>3</sup>(n)</th> <th>Σ</th> </tr> </thead> <tbody> <tr> <td>no</td> <td>yes</td> <td>22(36.7%)</td> <td>25(55.6%)</td> <td>47</td> </tr> <tr> <td>no</td> <td>no</td> <td>38(63.3%)</td> <td>20(44.4%)</td> <td>58</td> </tr> <tr> <td>yes</td> <td>yes</td> <td>3</td> <td>2</td> <td>5</td> </tr> <tr> <td>yes</td> <td>no</td> <td>15</td> <td>1</td> <td>16</td> </tr> </tbody> </table> <p>- Irrespective of MS, excellent pain relief in 16/32(50%) when <math>VB20 \geq 20mm^3</math> &amp; 14/52(27%) when <math>VB20 &lt; 20mm^3</math> (<math>p=0.038</math>)</p> <p>- Excellent result significantly correlated with absence of MS (<math>p=0.047</math>) when independent variables = age, laterality, sex, history of TN surgery, interval fr. 1st symptom.</p> <p>Multivariate analysis : -Excellent pain relief at 6 &amp; 12 mo significantly correlated with <math>VB20 \geq 20mm^3</math> (<math>p=0.018</math>) -No statistical correlation btw. <math>VB20</math> &amp; <math>VB50</math> &amp; the excellent &amp; good results at 6 &amp; 12 mo. -A <math>VB20</math> of <math>20mm^3</math> <math>&gt;</math> likely in the absence of MS (45/105 patients=43%) vs. with MS (3/21=14%)</p> <p>When the 4mm isocentre was placed on the trigeminal nerve so that 50% isodose line touched the brainstem, <math>VB20</math> was significantly higher (<math>p=0.003</math>) on the right than left side TN.</p> <p>There was an inverse relationship btw. <math>VB20</math> &amp; <math>VT50</math> (<math>p=0.01</math>) <math>\Rightarrow</math> a smaller vol. of the nerve is covered by the radiosurgical target as it is placed closer to the brainstem <math>\Rightarrow</math> it would seem that for a fixed dose, the proximity of the target to the brainstem is <math>&gt;</math> important for pain relief than a more distal placement that would increase the nerve vol. treated.</p>	MS	Excellent	VB20<20mm <sup>3</sup> (n)	VB20≥20mm <sup>3</sup> (n)	Σ	no	yes	22(36.7%)	25(55.6%)	47	no	no	38(63.3%)	20(44.4%)	58	yes	yes	3	2	5	yes	no	15	1	16	MS	Excellent	VB20<20mm <sup>3</sup> (n)	VB20≥20mm <sup>3</sup> (n)	Σ	no	yes	22(36.7%)	25(55.6%)	47	no	no	38(63.3%)	20(44.4%)	58	yes	yes	3	2	5	yes	no	15	1	16	<p>Data suggest :</p> <p>(1) excellent results <math>&gt;</math> likely as <math>VB20 \uparrow</math> and especially when <math>VB20 \geq 20mm^3</math>.</p> <p>(2) pain relief in patients with MS-TN is <math>&lt;</math> likely vs. those without TN after GKS and in patients with MS, the isocentre tended to be farther from the brainstem than in other patients. Placing the isocentre closer to the brainstem might improve the results.</p> <p>(3) there appears to be different dose-vol calculated on the left and right sides during GKS even when same isodose is placed tangential to the brainstem (tendency for <math>VB20 &gt;</math> on the right vs. left sides)</p>
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					At 6mo, 5/106 (4%) developed moderately troublesome dysaesthesias. All of them experienced complete pain relief. 4 of them developed dysaesthesias 375, 90, 545 & 270 days after GKS had VB20s of 0mm <sup>3</sup> , 11.5mm <sup>3</sup> , 30.1mm <sup>3</sup> & 44.1mm <sup>3</sup> , respectively. The fifth patient developed dysaesthesias at 285 days after 1st GKS & 118 days after 2nd GKS(40Gy) had VB20 of 11.4mm <sup>3</sup> (1st GKS) & 20.7mm <sup>3</sup> (2nd GKS).																					
Brisman, 2000 <sup>23</sup>	Gamma knife surgery (GKS) B, a single 4mm collimator, targeting at the nerve root close to brainstem.  <b>Max D=</b> 75 Gy  <b>P1</b> = primary GKS <b>P2</b> = secondary GKS after other prior surgery  <b>Design:</b> case series, multinomial logistical regression, univariate & multivariate analysis	New York, May 1998-Feb2000  <b>In:</b> patients with TN, not adequately controlled with drugs  <b>Out:</b> -	<b>TN type:</b> Idiopathic TN patients:  <b>At beginning :</b> <b>N=126</b>  <b>P1=61</b> <b>P2=65</b>  <b>At end : N=84</b>  <b>Age: (mean/range)</b> -  <b>M/F:</b> -	<b>Prior surgery :</b> 65 P2 patients at FU of 6 mo had a total of 153 prior surgeries (11 mVD, 135 percutaneous with radiofrequency, glycerol or both, 5 peripheral neurectomies, 1 subtemporal operation : & 1 tractomy  <b>FU:</b> either by mail or phone interview, a standardised questionnaire administered by an assistant at 6mo in 126 patients & 12mo in 84 patients  <b>Primary:</b> efficacy of GKS as 1st procedure - pain response defined as excellent (no pain, no drug), good(>=50% improvement, occasional pain & no drug or 50-100% pain relief & drug that didn't induce discomfort). <b>Adverse effects:</b> complications	<b>1) facial pain outcomes</b> - Excellent or good pain relief > likely in P1 vs. P2 in multivariate analysis (p=0.058) and univariate analysis (p=0.025) at 6 & 12 mo (p=0.051). This analysis was also performed for age (p=0.482), laterality (p=0.963), sex (p=0.482), interval fr. 1st symptom to GKS (p=0.674), & absence of MS (p=0.042) as independent variables - No difference in excellent result alone P1vs.P2 at 6 (p=0.844) & 12 mo(p=0.452) <table border="1"><thead><tr><th>FU</th><th>MS</th><th>P1(%)</th><th>P2(%)</th></tr></thead><tbody><tr><td>6mo</td><td>no</td><td>44/49(89.8)</td><td>40/56(71.4)</td></tr><tr><td>12mo</td><td>no</td><td>23/27(85.2)</td><td>33/42(78.6)</td></tr><tr><td>6mo</td><td>yes</td><td>9/12(75)</td><td>4/9(44.4)</td></tr><tr><td>12mo</td><td>yes</td><td>4/7(57.1)</td><td>3/8(37.5)</td></tr></tbody></table> - Within P2, the likelihood of an excellent or good result at 6 mo not affected by no. of prior surgeries, the interval for last procedure to GKS, a prior MVD or a prior percutaneous procedure. - The interval btw 1st symptom & GKS shorter in P1 vs. P2, esp.ly with MS-TN. Whereas, the mean for TN without MS = 87 mo (P1) vs 148 mo (P2) (p=0.004). The mean for MS-TN was 44 mo(P1) vs 147 mo (P2) (p=0.001). - P1 has a younger mean age vs. P2 (56.5 vs. 65.1)  <b>2) Division of TN (V1=ophthalmic, V2=maxillary &amp; V3=mandibular)</b> - Although no significant diff. btw P1 & P2 in division of pain (p=0.244) in non-MS patients, there is a tendency for isolated V3 involvement to occur more often in P2 (23/56=41%) vs. P1(14/49=28%); and isolated V2 in P1 (16/49=32%) vs. P2 (12/56=21%). - There is a tendency for excellent or good 6mo results to occur > in all patients without MS who had V1 involvement (68/88=77%) (p=0.108).  <b>3) Complications</b>	FU	MS	P1(%)	P2(%)	6mo	no	44/49(89.8)	40/56(71.4)	12mo	no	23/27(85.2)	33/42(78.6)	6mo	yes	9/12(75)	4/9(44.4)	12mo	yes	4/7(57.1)	3/8(37.5)	Study assessing GKS as a primary vs. secondary management of TN.  21 MS-TN patients.  Data suggest : (1) patients without prior surgery fare better after GKS vs. those with prior surgeries, but this improvement is seen for excellent and good results, and not for excellent results alone. (2) MS-TN patients < likely to experience pain relief than those without MS. A tendency (not significant) for MS-TN patients without prior surgery to benefit > often from GKS vs. those with prior surgery. No dysaesthesias found in patients with MS-TN, although uncommon in all patients. (3) GKS seems to fare better in those with V1 pain either alone or in combination (94% had pain relief, p=0.14) without apparent corneal denervation.  Conclusion : GKS as primary management seems to give better pain relief at 6 & 12 mo than when it is used as secondary management (for excellent & good results
FU	MS	P1(%)	P2(%)																							
6mo	no	44/49(89.8)	40/56(71.4)																							
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					<ul style="list-style-type: none"> <li>- At 6mo, 2 P1 patients developed moderately troublesome dysaesthesias at 90 &amp; 270 days &amp; 2 P2 patients at 375 &amp; 575 days post-GKS. .</li> <li>- Another patient developed dysaesthesias 4 mo after 2nd GKS(40Gy) and 9.5 mo after 1st GKS.</li> <li>- All patients with new dysaesthesias had TN without MS and all had complete pain relief.</li> <li>- No cases of anaesthesia dolorosa, 5th cranial nerve motor dysfunction, corneal denervation or keratitis.</li> </ul>	combined, but not on excellent results alone)
Pollock et al., 2000 <sup>24</sup>	<p>Gamma knife surgery (GKS), Model B Leksell gamma knife, targeted at the proximal nerve root as it existed the brainstem.</p> <p><b>D=</b> Max = 70Gy The dosimetry of the repeated GKS included 70Gy with 1 shot (1 patient), 70Gy with 2 shots (1 patient), 80Gy with 1 shot (1 patient), 90Gy with 1 shot (6 patients), &amp; 120Gy with 1 shot (1 patient).</p> <p><b>Design:</b> single-blind (assessors in FU), case series</p>	<p>Mayo clinic, apr 97-dec 99</p> <p><b>In:</b> patients with recurrent pain after first GKS, achieved a significant reduction in their pain after 1st GKS (excellent, good or fair outcomes)</p> <p><b>Out:</b> others</p>	<p><b>TN type:</b> essential neuralgia</p> <p><b>At beginning</b> N = 10</p> <p><b>Age:</b> <u>(mean/range)</u> 68(48-83)</p> <p><b>M/F:</b> n/a</p>	<p><b>Mean time to repeated GKS =</b> 13mo (4-27)</p> <p><b>Period FU (med) =</b> 15mo (3 - 32mo)</p> <p><b>Primary:</b> facial pain outcomes defined as excellent (pain-free, no medications), good (pain-free, medications req. at decreased dose), fair (significantly less pain, medications req. at a decreased dose, patient would repeat procedure to obtain this level of pain control), &amp; poor (no significant change in pain, patient would not repeat procedure to obtain this level of control).</p> <p><b>Adverse effects:</b> complication</p>	<p><b>1) Pain relief</b></p> <ul style="list-style-type: none"> <li>- 9 of 10 patients were pain free at median = 2 wks after repeated GKS (1-4 wks).</li> <li>- 1 patient had a pain recurrence 3 mo after repeated GKS. This patient had a total of 5 operations including MVD and had refused further surgery.</li> <li>- 1 patient was hospitalised at the time of the 2nd GKS, requiring intravenously administered fluids and narcotic agents. Also underwent MVD, percutaneous procedure. Repeated GKS performed at 120Gy. No improvement in pain.</li> <li>- Overall, 8 patients remained pain free without medication (excellent) at median FU=15 mo.</li> </ul> <p><b>2) Complication/adverse effects</b></p> <ul style="list-style-type: none"> <li>- All 8 patients with continued excellent result developed new facial numbness (6), paraesthesias (2).</li> <li>- Anaesthesia dolorosa not observed in any patients.</li> </ul>	<p>Study assessing efficacy of repeated GKS and used a greater radiation dose to the same target at the 2nd GKS than the 1st. They found :</p> <p>(1) 8 of 10 patients underwent repeated GKS remained pain-free and medication-free up to median FU of 15 mo</p> <p>(2) all 8 patients sustained some degree of trigeminal dysfunction. Authors believed that this data support the argument against a selective effect of GKS on different afferent fiber types. Instead, a correlation btw pain relief and facial numbness or paraesthesias suggests that GKS injures both myelinated and unmyelinated fibers in a non-selective manner comparable to RFR.</p> <p>Authors emphasised that dose selection in GKS must balance the goals of pain relief and the preservation of normal nerve function.</p>
Hasegawa et al., 2002 <sup>25</sup>	<p>Gamma knife surgery (GKS), Leksell gamma knife Model B or U, a single 4mm isocentre. Target was placed anterior to the</p>	<p>Pittsburgh, since 1997</p> <p><b>In:</b> patients with recurrent pain after first GKS, achieved a significant</p>	<p><b>TN type:</b> idiopathic &amp; typical TN</p> <p><b>At beginning</b> N = 31</p> <p><b>At end, N =</b> 27</p>	<p><b>Pain duration(mean) :</b> 10.4(1-27)</p> <p><b>No. patients with prior surgery before 1st GKS:</b> 22 (81.5%) and 13% had experienced some degree of facial sensory changes.</p>	<p><b>1) Facial pain relief</b></p> <p>A 2nd GKS provides &gt;50% pain relief (complete &amp; partial) in 85% of patients. This data is fairly consistent with outcomes of 1st GKS although fewer patients achieved complete relief and could discontinue medication.</p> <p><u>Outcomes</u>                      1st GKS      2nd GKS</p> <p>Result</p>	<p>These patients represented a medically and surgically refractory group who had not had a satisfactory response to medication and who had undergone an average of almost 2 ops. before 1st GKS.</p>

	<p>first GKS target so that the two radiosurgical vol. overlapped by 50%. This way the brainstem receives less radiation than at 1st GKS &amp; an additional length of the nerve would be irradiated.</p> <p><b>Mean D (max)=</b> 64.4 (50 to 80) Gy (vs. 75.6Gy at 1st GKS, 60-90 Gy)</p> <p><b>Design:</b> case series, single-blind (assessor), statistical/kaplan-meier analysis</p>	<p>reduction in their pain after 1st GKS (excellent, good or fair outcomes)</p> <p><b>Out:</b> Tumour-related, MS-related, other pathological conditions (herpetic infection, lyme disease, wallenberg syndrome)</p>	<p><b>Age:</b> <b>(mean/range)</b> <b>D:</b> 68.7(33-85)</p> <p><b>Side of pain :</b> <b>Right/Left =</b> 15/12</p> <p><b>M/F:</b> <b>D:</b> 8/9</p>	<p><b>Mean prior surgery before 1st GKS =</b> 1.8(0-7)</p> <p><b>Interval 1stGKS to 2ndGKS (mean,mo) =</b> 22.3(6-73)</p> <p><b>FU:</b> patients' self-assessed with blinded assessor via telephone interview).</p> <p><b>Mean FU (mo) =</b> 22(6-78)</p> <p><b>Primary:</b> pain relief - poor/failure (no pain relief or &lt;50% relief), fair (partial relief, &gt;50%), good (complete relief but still on medications), excellent (100% pain free, no medication).</p> <p>Good response category includes those patient who had complete pain relief but continue with medication for fear of recurrent pain.</p> <p><b>Adverse effects:</b> complications</p>	<table border="0"> <tr> <td>Excellent</td> <td>13 (48.1%)</td> <td>5 (18.5%)</td> </tr> <tr> <td>Good</td> <td>3 (11.1%)</td> <td>8 (29.6%)</td> </tr> <tr> <td>Fair</td> <td>7 (25.9%)</td> <td>10 (37%)</td> </tr> <tr> <td>Poor</td> <td>4 (14.8%)</td> <td>4 (14.8%)</td> </tr> </table> <p>Relief</p> <table border="0"> <tr> <td>Complete</td> <td>16 (59.3%)</td> <td>13 (48.1%)</td> </tr> <tr> <td>Complete &amp; partial (&gt;50%)</td> <td>23 (85.2%)</td> <td>23 (85.2%)</td> </tr> </table> <p>Facial sensory symptoms (\$ all 4 patients had additional surgeries-glycerol and RF rhizotomy, * actuarial calculation)</p> <p>2 (7.4%)      3 (12.7%)*</p> <p><b>2) Recurrence</b></p> <ul style="list-style-type: none"> <li>- Mean time to recurrence after 1st GKS = 18.2 mo (3-64)</li> <li>- Mean time to recurrence after 2nd GKS = 5.5 mo(3-9) with 4 of 23 patients achieving &gt;50% relief had recurrent pain within 3, 5, 5, or 9 mo. All 4 patients (17.4%) worsened after an initial fair result.</li> <li>- No difference observed for high and low dose of irradiation and the onset of recurrence</li> <li>- Durability of complete or partial pain relief = 70.1% at 1 year.</li> <li>- At 6mo &amp; at 12mo, 81.4(±2.6)% &amp; 85.6(±2.47)% patients respectively achieved &gt;50% relief.</li> <li>- At 6mo &amp; at 12mo, 64.9(±3.2)% &amp; 70.3(±3.16)% patients respectively achieved complete relief (excellent&amp; good) and by 33 mo, 75.4(±3.16)%.</li> <li>- Multivariate analysis suggested the rate of relief for patients with typical TN faster vs. patients with additional atypical pain. No significant difference was found in this factor.</li> </ul> <p><b>3) Complications</b></p> <ul style="list-style-type: none"> <li>- 2 patients had new sensory symptoms after 1st GKS.</li> <li>- 3 patients (11.1%) had new sensory symptoms after 2nd GKS.</li> <li>- A higher risk of sensory disturbance after 2nd GKS than 1st GKS. The actuarial data of developing new sensory symptoms = 12.7% (2nd GKS) vs. 7.4% (1st GKS).</li> <li>- No relationship found btw. radiosurgical dose &amp; onset of sensory changes</li> <li>- No other complication found.</li> </ul>	Excellent	13 (48.1%)	5 (18.5%)	Good	3 (11.1%)	8 (29.6%)	Fair	7 (25.9%)	10 (37%)	Poor	4 (14.8%)	4 (14.8%)	Complete	16 (59.3%)	13 (48.1%)	Complete & partial (>50%)	23 (85.2%)	23 (85.2%)	<p>A preponderance of patients who are afraid to discontinue medication completely esp.ly after 2nd GKS.</p> <p>Radiation dose is lower in 2nd GKS, boosting the effect of 1st GKS.</p> <p>Conclusion :</p> <ol style="list-style-type: none"> <li>(1) 1st GKS is as effective as 2nd GKS.</li> <li>(2) higher risk of sensory disturbance after 2nd GKS vs. 1st GKS</li> <li>(3) a decreased dose of irradiation (2nd GKS) resulted in less patients obtaining complete relief without medication, but better preservation of facial sensation.</li> </ol>
Excellent	13 (48.1%)	5 (18.5%)																						
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Kannan et al., 1998 <sup>26</sup>	Gamma knife surgery (GKS), Laskell gamma	Mumbai, India, Jan 97-Jan 98	<b>TN type:</b> idiopathic TN (6) & 1 bilateral	<b>Pain duration :</b> 3-10 year <b>No. patients with prior</b>	<b>1) Facial pain relief</b> Complete relief = 4 patients Poor relief = 2	Only 1 of 7 patients had a prior operation, i.e. MVD 3 yrs before this GKS was																		

	<p>knife Model a single 4mm isocentre, 2-4 mm anterior to the nerve junction with the pons.</p> <p><b>D</b> = 70 Gy (3 patients) to 80 Gy (4 patients)</p> <p><b>Design:</b> case series</p>	<p><b>In:</b> TN patients with functional disorder and bilateral neuralgia</p> <p><b>Out:</b> Tumour-related, vascular disorders</p>	<p>neuralgia</p> <p><b>At beginning</b> <b>N</b> = 7 <b>At end, N</b> = 7</p> <p><b>Age:</b> <b>(mean/range)</b> <b>D:</b> 56(42-79)</p> <p><b>M/F:</b> <b>D:</b> 5/1 (detail of 1 patient not given)</p>	<p><b>surgery</b> : 1 (MVD)</p> <p><b>FU:</b> until May 1998</p> <p><b>Median FU (mo)</b> = 10 (5-16)mo</p> <p><b>Primary:</b> pain relief assessed as complete relief and poor relief (no definition given on this)</p> <p><b>Adverse effects:</b> complications</p>	<p>- Latency period to pain relief = 4-12 wks. - No pain relapse or exacerbation in all patients during FU.</p> <p><b>2) Complications</b> - No complication observed in the 10 mo FU.</p>	<p>performed.</p> <p>GKS targeting the trigeminal root entry zone at a dose of 70-80Gy appears to be a safe and effective non-invasive therapy for medically refractory patients.</p>										
Han et al., 1999 <sup>27</sup>	<p>single 4mm isocentre, centered over the t/nerve at its root entry zone, 50% isodose to brainstem</p> <p><b>D</b>= 70Gy (36 patients) &amp; 80Gy (last 7 patients)</p> <p><b>Design:</b> case series,</p>	<p>Barrow Neurological Institute</p> <p><b>In:</b> idiopathic TN, refractory to medications, MS-TN, with/without prior surgery</p> <p><b>Out:</b> tumour-related</p>	<p><b>At beginning, N</b>=43</p> <p><b>Age (mean):</b> 66</p> <p><b>M/F:</b> 25/18</p>	<p><b>Pain duration(yrs)</b> = 10.9</p> <p><b>Prior surgery (no.patient):</b> 22 underwent a total of 46 procedures</p> <p><b>FU:</b> postal standardised questionnaire</p> <p><b>Mean FU (mo)</b> = 9 mo (2-23)</p> <p><b>Primary:</b> pain relief - excellent (no pain &amp; no drugs), good (occasional pain, no drug), fair (pain improvement, well control on drug), failure (improved pain but not yet controlled on drug &amp; no pain relief)</p> <p><b>Adverse effects:</b> complications</p>	<p><b>(1) Pain relief</b> - 77% patients achieved at least fair result. - Mean time to initial pain relief = 31 days (1-115) - Mean time to maximal relief = 78 days.</p> <table border="1"> <thead> <tr> <th><u>Pain relief</u></th> <th><u>No.patients</u></th> </tr> </thead> <tbody> <tr> <td>Excellent</td> <td>15(35%)</td> </tr> <tr> <td>Good</td> <td>3(7%)</td> </tr> <tr> <td>Fair</td> <td>15(35%)</td> </tr> <tr> <td>Failure</td> <td>10(23%)</td> </tr> </tbody> </table> <p><b>(2) Complications</b> - New facial numbness but not bothersome = 3 (7%)</p>	<u>Pain relief</u>	<u>No.patients</u>	Excellent	15(35%)	Good	3(7%)	Fair	15(35%)	Failure	10(23%)	<p>Study reported initial results.</p> <p>GKS appears to have minimal morbidity. More patients and longer FU needed.</p>
<u>Pain relief</u>	<u>No.patients</u>															
Excellent	15(35%)															
Good	3(7%)															
Fair	15(35%)															
Failure	10(23%)															

## Appendix 4 Evidence from 3 recent studies on alternative techniques

Data extraction table of most recent studies on alternative techniques

Authors, year	Treatment type. Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patient - TN type, number, age mean± SD (range), male/female, ethnicity	Pain duration, type & no. prior surgery, follow-up mean (range), Outcomes	Results	Comments												
Sindou, 2000 <sup>28</sup>	MVD  Design : case series	In ; idiopathic TN, Out : tumour-related	<b>At beginning</b> N= 322 idiopathic TN patients  <b>At end</b> N = 300 (as 22 had partial section and therefore excluded)  Age : n/s M/F : n/s	<b>Pain duration</b> : n/s  <b>Prior surgery</b> : n/s  <b>FU</b> : 1 - 14 years (mean= 6yrs)  <b>Outcomes</b> : pain relief (total, good, fair, dissociated cure, failure), recurrence and complications	<b>1) Pain relief</b> - 2 patients (0.6%) died fr. haemorrhagic infarction of the cerebellum - 7 (2.3%) had immediate failure and referred for PRFR. - 250 (83.8%) had total pain relief and 25 (8.3%) suffered from episodic crises but didn't require medication - 12 (4%) had incomplete improvement 4 (1.3%) had 'dissociated' cure (with complete relief of paroxysmal crises but not permanent burning component). - For the 250 patients with total relief, complete pain relief was obtained immediately after surgery for 75% patients and the remaining 25% achieved complete relief weeks or months after.  <table border="0"> <tr> <td><u>pain outcomes</u></td> <td style="text-align: right;"><u>%</u></td> </tr> <tr> <td>complete relief</td> <td style="text-align: right;">83.8</td> </tr> <tr> <td>good relief (episodic crises, no drug)</td> <td style="text-align: right;">8.3</td> </tr> <tr> <td>fair result (incomplete improvement, drug)</td> <td style="text-align: right;">4.0</td> </tr> <tr> <td>dissociated cure</td> <td style="text-align: right;">1.3</td> </tr> <tr> <td>failure</td> <td style="text-align: right;">2.6</td> </tr> </table> - Patients with paroxysmal pain had a better result than those with paroxysmal and continuous pain (p<0.001). - Patients with pain extending to 2 or 3 branches responded less favourably than those with 1 branch (p<0.05)  <b>2) Recurrence</b> : - Of the 291 who had effective pain relief, 14% had a recurrence after a 1 to 12 years FU (ave = 5 yrs). In 75% of these patients, recurrence occurred within the first post-op year.	<u>pain outcomes</u>	<u>%</u>	complete relief	83.8	good relief (episodic crises, no drug)	8.3	fair result (incomplete improvement, drug)	4.0	dissociated cure	1.3	failure	2.6	MVD is the best, at least for patients with good general health when the surgeon is experienced with MVD.
<u>pain outcomes</u>	<u>%</u>																	
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					<p><b>3) Complications :</b></p> <p><b>Neurological</b> %</p> <p>Ischaemic syndrome (superior cerebellar artery territory) : 0.7</p> <p>2 patients with death (0.35)</p> <p>2 patients with permanent deficits (0.35)</p> <p>Venous congestion/oedema (severe) 0.2</p> <p>Facial weakness(permanent) 0.3</p> <p>Hearing loss - transient 1.4</p> <p>Hearing loss - permanent 0.3</p> <p>Trochlear nerve palsy - transient 3.2</p> <p>Trochlear nerve palsy - permanent 0.3</p> <p>Trigeminal hypaesthesia - dysaesthesia 1.6</p> <p>Greater occipital neuralgia 0.3</p> <p><b>Surgical wound</b> %</p> <p>CSF leak 17.0</p> <p>Bacteria meningitis (cured by antibiotics) 3.1</p> <p>Serohaemorrhagic 'otitis' (with transient hearing decrease due to liquid in mid ear) 9.9</p> <p>Delayed wound healing (with need for reoperation) 0.6</p>																	
Kanpolat et al, 2001 <sup>29</sup>	PRFR  <b>Design :</b> case series, retrospective, kaplan-meier analysis of pain-free survival	Ankara University, Turkey, 1974-1999  <b>In:</b> idiopathic, typical TN, older patients, patients who didn't want MVD, patients with poor medical status, patients with medical refractory to carbamazepine up >800mg/day  <b>Out:</b> atypical, symptomatic, cluster headache, trigeminal neuropathic pain, tumour related	<b>At beginning</b> <b>N = 1600</b> , underwent 2138 PRFRs <b>At end</b> <b>N = 1600</b> (36 of 67 patients who had bilateral TN were treated with bilateral PRFR, 1216 successfully managed with a single procedure)  <b>Age: mean (range)</b> 56.83±13(15-99)  <b>M/E:</b> 766/834	<b>FU:</b> patient assessed pain level, questionnaire survey  <b>Mean FU (yrs) = 5.7±5.5 (1-25)</b>  <b>Primary:</b> facial pain outcomes defined as complete pain relief (pain-free, no medication), partial satisfactory(recurrence pain < severe than pre-op, controlled with drugs & no need for repeated PRFR), partial unsatisfactory relief, no change & worse.  <b>Adverse effects:</b> complications	<p><b>1) pain relief after PRFR (Kaplan meier analysis)</b></p> <p>- Initial acute pain relief in 1561 (97.6%).</p> <p>- In 719 patients followed for 5 years, 57.7% achieved complete pain control after a single PRFR, &amp; increased to 92% with multiple PRFRs.</p> <p>- In 365 patients followed for 10 years, 52.3% achieved complete pain control after a single PRFR.</p> <p>- In 39 patients followed for 20 years, 41% achieved complete pain control fr. a single PRFR</p> <p><b>2)recurrence</b></p> <p>- Early (&lt; 6 mo) pain recurrence in 123 (7.7%) patients vs. late recurrence (&gt;6mo) in 278 (17.4%).</p> <p>- Overall pain recurrence rate = 25.1% at average FU = 5.7±5.5 (1-25) years</p> <p><b>3) Complication/adverse effects</b></p> <table border="1"> <thead> <tr> <th>Complications</th> <th>Patients(%)</th> </tr> </thead> <tbody> <tr> <td>Anaesthesia dolorosa</td> <td>12(0.8)</td> </tr> <tr> <td>Painful dysaesthesia</td> <td>16(1.0)</td> </tr> <tr> <td>Absent corneal reflex</td> <td>91(5.7)</td> </tr> <tr> <td>Corneal keratitis</td> <td>10(0.6)</td> </tr> <tr> <td>Masseter paresis</td> <td>48(3.0)</td> </tr> <tr> <td>Masseter paralysis</td> <td>18(1.1)</td> </tr> <tr> <td>Transient cranial nerve paralysis</td> <td>12(0.75)</td> </tr> </tbody> </table>	Complications	Patients(%)	Anaesthesia dolorosa	12(0.8)	Painful dysaesthesia	16(1.0)	Absent corneal reflex	91(5.7)	Corneal keratitis	10(0.6)	Masseter paresis	48(3.0)	Masseter paralysis	18(1.1)	Transient cranial nerve paralysis	12(0.75)	PRFR is a minimally invasive and effective procedure that is especially indicated in older patients with idiopathic TN that is confined to the second and third branches. The procedure can be repeated easily if pain recurs.
Complications	Patients(%)																					
Anaesthesia dolorosa	12(0.8)																					
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					Oculomotor nerve 1 Abducens nerve 11 Permanent cranial nerve paralysis, abducens nerve 2(0.13) Cerebrospinal fluid leak 2(0.13) Carotid-cavernous fistula 1(0.06) Aseptic meningitis 1(0.06)	
Skirving & Noel, 2001 <sup>30</sup>	Percutaneous balloon compression (PBC), Mullan & Lichtor technique introduced in 1983  <b>Design:</b> case series	20 years (1980-1999)  <b>In:</b> typical, unilateral TN  <b>Out:</b> n/a	<b>At beginning</b> <b>N = 496</b>  <b>At end</b> <b>N = 496</b> (underwent 531 PBCs)  <b>Age: mean (range)</b> 66.7(34-88)  <b>M/F:</b> 1:0.76 ratio	<b>FU:</b> FU over a period of 2 yrs and questionnaire survey after (only 40 of 70 patients responded to Q/survey)  <b>Mean FU (yrs) = 10.7</b>  <b>Primary:</b> facial pain outcomes, recurrences rate  <b>Adverse effects:</b> complications	<b>1) pain relief after PBC</b> - 9 technical failures - 521 procedures with immediate pain relief - 1 procedure with failure to achieve pain relief  <b>2)recurrence of pain</b> - in the first 5 years, recurrence rate = 19.2% (95 patients) - in over series (mean=10.7yrs) = 31.9% (158 patients).  <b>3) Complication</b> - early tolerated facial numbness = 89%(441 patients) but persisted > 3 mo in 23 patients (4.6%) - symptomatic dysaesthesia = 3.8% (19) - temporary (recovered within 4 mo) symptomatic masseter weakness = 17 (3.4%) - temporary (recovered within 4 mo) diplopia secondary to cranial nerve dysfunction = 8 (1.6%) - 0 corneal anaesthesia and anaesthesia dolorosa and aseptic meningitis - 1 case, the balloon was dislodged fr. the end of the catheter, most likely catching and then tearing on the needle (no untoward symptoms)	Authors' literature review showed comparable efficacy of PBC results with those of radiofrequency lesioning and glycerol rhizotomy, with fewer adverse effects/complications

## Appendix 5 Unpublished evidence of gamma knife radiosurgery

(Data compiled by the National Centre for Stereotactic Radiosurgery, December 2003)

Authors, year	Treatment type and radiation dosage (D), isocentre (C) Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patient - TN type, number, age mean± SD (range), male/female, ethnicity	Pain duration, type & no. prior surgery, follow-up mean (range), Outcomes	Results	Comments																												
National Centre for Stereotactic Radiosurgery, Sheffield 2003 <sup>138</sup>	Gamma knife surgery (GKS), RBS Model (1996-2001) and Model C GK (2001- cont) Leksell gamma knife, output factor = 0.80, Single field 4mm collimator, targeted to REZ, 80Gy target dose  <b>Design:</b> retrospective case series analysis	National Centre for Stereotactic Radiosurgery, Sheffield  May 1996 to Dec 2001  Complete consecutive series 77pts, 64 in analysis (>1yr FU)  Incl: medically intractable	<b>TN type:</b> <b>Idiopathic 35 (no cause found)</b>  <b>Vasc: (Vessel compression seen): 12</b>  <b>MS: 6</b>  <b>Tumour compression (secondary): 5</b>  <b>Skull base anomaly: 2 (failed open surgery and ganglion inj)</b>  <b>Atypical facial pain: 4</b>	<b>No. prior surgery before GKS (mean no.): 0</b>  <b>FU: 11 months ± 5 months</b>  Patients instructed to continue perioperative medications till pain was gone and then to taper medications as tolerated over an interval of few weeks.  <b>Primary:</b> facial pain outcomes defined as excellent (pain-free, no medications), good (pain-free, medications req. at decreased dose), fair (significantly less pain, medications req. at a decreased dose, patient would repeat procedure to obtain this level of pain control), & poor (no significant change in pain, patient would not repeat procedure to obtain this level of pain control).  <b>Adverse effects:</b> complication	<table border="1" data-bbox="1211 536 1753 938"> <thead> <tr> <th></th> <th>Idiop.</th> <th>Vasc</th> <th>Tu</th> <th>MS</th> <th>Skull base anomaly</th> <th>Atyp</th> </tr> </thead> <tbody> <tr> <td>Excellent / Good</td> <td>23(66%)</td> <td>8(67%)</td> <td>1 (20%)</td> <td>3 (50%)</td> <td>2 (100%)</td> <td></td> </tr> <tr> <td>Fair (&gt;50% impr)</td> <td>6 (17%)</td> <td>2 (17%)</td> <td>3 (60%)</td> <td>1 (17%)</td> <td></td> <td>1 (25%)</td> </tr> <tr> <td>Poor (&lt;50% impr)</td> <td>6 (17%)</td> <td>2 (17%)</td> <td>1 (20%)</td> <td>1 (20%)</td> <td>2 (33%)</td> <td>3 (75%)</td> </tr> </tbody> </table> <p><b>Complications:</b> During the observation period one case of facial numbness in a patient with complete pain relief.</p>		Idiop.	Vasc	Tu	MS	Skull base anomaly	Atyp	Excellent / Good	23(66%)	8(67%)	1 (20%)	3 (50%)	2 (100%)		Fair (>50% impr)	6 (17%)	2 (17%)	3 (60%)	1 (17%)		1 (25%)	Poor (<50% impr)	6 (17%)	2 (17%)	1 (20%)	1 (20%)	2 (33%)	3 (75%)	<b>Conclusions:</b> <ol style="list-style-type: none"> <li>atypical facial pain is not treated any more.</li> <li>absence of visible vascular compression <b>not</b> contraindication and results are similar to those with MRI demonstrated compression</li> <li>previous surgery of any kind reduced the success rate</li> </ol>
	Idiop.	Vasc	Tu	MS	Skull base anomaly	Atyp																												
Excellent / Good	23(66%)	8(67%)	1 (20%)	3 (50%)	2 (100%)																													
Fair (>50% impr)	6 (17%)	2 (17%)	3 (60%)	1 (17%)		1 (25%)																												
Poor (<50% impr)	6 (17%)	2 (17%)	1 (20%)	1 (20%)	2 (33%)	3 (75%)																												

## Appendix 6 Evidence on atypical TN and multiple sclerosis TN patients

Data extraction table of one study comparing atypical TN and typical TN after MVD treatment

Authors, year	Treatment type. Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patient - TN type, number, age mean± SD (range), male/female, ethnicity	Pain duration, type & no. prior surgery, follow-up mean (range), Outcomes	Results	Comments
Tyler-Kabara et al, 2002 <sup>31</sup>  Atypical vs. typical TN  MVD	MVD <b>M1</b> = No. of MVD in patients with typical TN <b>M2</b> = No of MVD in patients with atypical TN  <b>Design</b> : case series, retrospective	University Hospital, Pittsburgh, Feb1972-Dec03  <b>In:</b> typical TN and atypical TN  <b>Out:</b> n/s	<b>At beginning, N</b> = 2264 patients  <b>At end, N</b> = 2264 <b>M1</b> = 2003 in 1739 patients (240 patients underwent multiple MVDs) <b>M2</b> = 672 in 537 patients (114 had multiple MVDs)  <u><b>Age: med (range)</b></u> 55(5-87)  <u><b>M/F:</b></u> 883/1381	<b>Pain duration (yr): median</b> = 6(<1-44)  <b>FU:</b> patient assessed pain level, questionnaire survey, telephone  <b>Mean FU (yrs)</b> = 11.3(5-22.6) for 974 patients <b>Median FU (yrs)</b> = 10.3 (974 patients)  <b>Primary:</b> facial pain outcomes defined as excellent (pain free, no medication), good (infrequent pain with low doses of medication), & poor (pain remained, on or off medication).  <b>Adverse effects:</b> complications	<b>1) Pain relief(immediate, post-op, long-term)*</b> <u>Pain relief result\$</u> <u>Typical(M1,%)</u> <u>Atypical(M2,%)</u> Immediate post-op. (all patients) excellent                    80.3                    46.9 good                         16.5                    39.7 poor                         3.2                     13.4 post-op (≥5yrs)+ excellent                    84.1                    58.2 good                         14.1                    33.2 poor                         1.8                     8.6 long-term outcome (≥5yrs) excellent                    73.7                    34.7 good                         6.8                     16.4 poor                         19.5                    48.9  * ≥ 5 yrs of FU for 969 of the typical cases & in 219 of atypical ones. \$ p<0.001 + only for patients available for FU after 5 years (974 typical TN patients & 220 atypical TN patients)  - Trigger points and memorable onset of pain +vely predicting excellent outcomes for both typical and atypical TN (p<0.05) - Preoperative sensory loss, previous MVD & previous destructive lesioning are -ve predictor for long-term pain relief (p=0.001 M1, p<0.05 M2) - Only trigger points were +ve predictors for good long-term outcomes whereas bilateral pain was -ve predictor of excellent outcomes (p=0.001).  <b>2) Complications</b> - The most notable difference btw complications for MVD in patients with typical and atypical TN surgery was the much higher rate of significant meningismus. (M1>M2 for meningismus)	Paper comparing atypical vs. typical TN after MVDs.  MVD is a safe and effective treatment for typical TN.  Study found extremely poor results for atypical TN. Despite post-op pain relief in 86% of patients, only 51% had long-term relief and only 35% had excellent long-term outcomes. These results are consistent with authors' belief that there is a group of patients along the continuum of typical to atypical TN who may benefit from MVD, referred as transitional TN patients (a subset of atypical patients with better outcomes).

					<table border="1"> <thead> <tr> <th rowspan="2">Complications</th> <th colspan="2">No. diagnosis (%)</th> </tr> <tr> <th>M1</th> <th>M2</th> </tr> </thead> <tbody> <tr> <td>death</td> <td>4(0.2)</td> <td>1(0.1)</td> </tr> <tr> <td>haematoma</td> <td>3(0.1)</td> <td>3(0.4)</td> </tr> <tr> <td>oedema</td> <td>9(0.4)</td> <td>6(0.9)</td> </tr> <tr> <td>infarction*</td> <td>2(0.1)</td> <td>6(0.9)</td> </tr> <tr> <td>hydrocephalus</td> <td>3(0.1)</td> <td>0</td> </tr> <tr> <td>palsy</td> <td></td> <td></td> </tr> <tr> <td>  CN VII</td> <td>34(1.7)</td> <td>6(0.9)</td> </tr> <tr> <td>  CN VIII</td> <td>29(1.4)</td> <td>7(1.0)</td> </tr> <tr> <td>  other CN\$</td> <td>93(4.6)</td> <td>16(2.4)</td> </tr> <tr> <td>CSF leak\$</td> <td>33(1.6)</td> <td>24(3.6)</td> </tr> <tr> <td>pseudomeningocoele</td> <td>5(0.2)</td> <td>3(0.4)</td> </tr> <tr> <td>meningitis</td> <td>5(0.2)</td> <td>5(0.7)</td> </tr> <tr> <td>meningismus\$</td> <td>257(12.8)</td> <td>146(21.7)</td> </tr> </tbody> </table> <p>*CN=cranial nerve; CSF=cerebrospinal fluid \$ p&lt;0.01 for comparison btw M1 &amp; M2</p>	Complications	No. diagnosis (%)		M1	M2	death	4(0.2)	1(0.1)	haematoma	3(0.1)	3(0.4)	oedema	9(0.4)	6(0.9)	infarction*	2(0.1)	6(0.9)	hydrocephalus	3(0.1)	0	palsy			CN VII	34(1.7)	6(0.9)	CN VIII	29(1.4)	7(1.0)	other CN\$	93(4.6)	16(2.4)	CSF leak\$	33(1.6)	24(3.6)	pseudomeningocoele	5(0.2)	3(0.4)	meningitis	5(0.2)	5(0.7)	meningismus\$	257(12.8)	146(21.7)	
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Resnick et al, 1996 <sup>76</sup> MS-TN patients MVD	3 pts underwent MVD alone and 2 pts had MVD plus partial section  Design : case series	In : 5 MS TN pts (3 had multiple unsuccessful percutaneous procedures and 2 in whom the diagnosis of MS had not been established, underwent exploration of the cerebellopontine angle	<b>N</b> = 5 MS TN patients	Primary : Pain relief Complication	<p>Patient 1 (MVD alone) - failure at 4 mo, CSF leak, dysaesthetic pain V3 Patient 2 (MVD + partial section) - pain free on carbamazepine Patient 3 (MVD + partial section) - pain free, no drug (cure) Patient 4 (MVD) - 23 mo pain free, then recurrence Patient 5 (MVD) - 24 mo pain free, then recurrence</p> <p>Complication : Slight hypaesthesia in V2 and V3 = 1 pt Dysaesthesia and csf leak = 1 pt</p>	Partial rhizotomy with MVD produced more encouraging results than MVD alone.																																												
Mizuno et al., 2000 <sup>77</sup> Atypical vs. typical TN	PBC  Design : case report	Nagaya, Japan  In : atypical TN, typical TN, patients over 70 year old	<b>N1</b> = 9 typical TN patients <b>N2</b> = 6 atypical TN patients  M/F : 5/10	<b>Prior surgery</b> :MVD in 4 pts and peripheral nerve block = 4 pts  FU = last FU at 24 mo  Primary: facial pain(100%, 75%, 50%, <50% pain relief)  Adverse effects : complications	<p><b>Initial pain outcome</b></p> <ul style="list-style-type: none"> <li>- 10 patients had complete relief immediately after PBC and 5 had 50% to 75% pain relief.</li> <li>- 3 of the 10 patients with complete pain relief were atypical TN pts and the other 3 atypical pts achieved 50% pain relief.</li> </ul> <p><b>Complications</b></p> <ul style="list-style-type: none"> <li>- 4 pts developed mild to moderate ipsilateral hemifacial numbness. In 3 pts., this disappeared in 3 mo.</li> <li>- 2 pts developed herpes simplex perioralis 1 wk after treatment</li> <li>- 2 pts developed hypertension during PBC treatment, and 1 pts encountered small amount of subarchnoid venous bleeding in the posterior fossa</li> </ul>	<p>PBC was effective with all the 6 atypical patients in this study.</p> <p>PBC could relieve atypical TN, typical TN in elderly patients and recurrent neuralgia following MVD.</p>																																												

					<b>Recurrence</b> <ul style="list-style-type: none"><li>- late recurrence in 2 patients (1 postherpetic pt at 3 mo and 1 typical TN pt at 24 mo)</li><li>- recurrence rate per year = 7.1%, mean recurrence-free interval = 30 mo. Severity and duration of attack was &lt; than before PBC treatment.</li></ul>	
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## Appendix 7 Type of complications after gamma knife surgery

### Type of complications after GKS treatment (number of patients)

Authors	New/ worsened TN dysfunction	Facial numbness - TN deficits	Tolerable hyperesthesias	Tolerable paresthesia	Bothersome/ Severe paresthesia	Bother-some dysesthesias	Deafness	Corneal numbness	Loss of taste	Other cranial nerve deficits
Pollock et al, 2001 <sup>6</sup>	26	35	0	0	0	0	0	0	0	0
Regis et al, 1999 <sup>7</sup>	0	0	0	0	0	0	0	0	0	0
Nicol et al, 2000 <sup>8</sup>	0	7	0	0	0	0	0	0	4	0
Pollock et al, 2002 <sup>9</sup>	1	43	0	19	0	14	0	3	0	2
Young et al, 1998 <sup>10</sup>	1	3 (delayed)	0	0	0	0	0	0	0	0
Rogers et al,2000 <sup>11</sup>	0	9 (delayed, partial)	0	0	0	0	0	0	0	0
Rogers et al, 2002 <sup>12</sup>	0	0	5	0	0	0	0	0	0	0
Maesawa et al., 2001 <sup>13</sup>	0	17	0	0	0	0	1	0	0	0
Kondziolka et al, 1996 <sup>14</sup>	0	0	0	0	0	0	0	0	0	0
Kondziolka et al, 1997 <sup>15</sup>	0	0	0	2 (increased paraesthesias, not bothersome)	0	0	0	0	0	0
Kondziolka et al, 1998a <sup>16</sup>	0	0	0	0	0	0	0	0	0	0
Kondziolka et al, 1998b <sup>17</sup>	12 new/increased paraesthesias & numbness	0	0	0	0	0	0	0	0	0
Kondziolka et al 2002 <sup>18</sup>	17 minor increased paraesthesias &/or numbness	0	0	0	0	0	1	0	0	0
Flickinger et	21	11	0	9	1	0	0	0	0	0

al, 2001 <sup>19</sup>										
Zheng et al, 2001 <sup>20</sup>	0	9	0	0	0	0	0	0	0	0
Urgosik et al, 1998 <sup>21</sup>	3 tactile hypaesthesia, 5 with thermal/algescic sensation impairments	0	0	0	0	0	0	0	0	0
Brisman & Mooij, 2000 <sup>22</sup>	0	0	0	0	0	5	0	0	0	0
Brisman, 2000 <sup>23</sup>	0	0	0	0	0	5				0
Pollock et al, 2000 <sup>24</sup>	0	6	0	2	0	0	0	0	0	0
Hasegawa et al, 2002 <sup>25</sup>	2 after 1st GKS 3 after 2nd GKS	0	0	0	0	0	0	0	0	0
Kannan et al, 1998 <sup>26</sup>	0	0	0	0	0	0	0	0	0	0
Han et al, 1999 <sup>27</sup>	0	3	0	0	0	0	0	0	0	0
National Centre for Stereotactic Radiosurgery, 2003 <sup>137</sup>	0	1	0	0	0	0	0	0	0	0