Stereotactic radiosurgery for primary trigeminal neuralgia: state of the evidence and recommendations for future reports

B C Lopez, P J Hamlyn, J M Zakrzewska

Objective: To identify systematically all the studies reporting outcomes and complications of stereotactic radiosurgery for trigeminal neuralgia and to evaluate them against predefined quality criteria.

Methods: Inclusion criteria for outcome analysis included thorough demographic documentation, defined diagnostic and outcome criteria, a minimum of 30 patients treated with 12 months median/mean follow up, not more than 20% lost to follow up, Kaplan–Meier actuarial analysis, primary trigeminal neuralgia, not more than 10% of patients retreated for failure or early recurrence, and minimum dose of 70 Gy.

Results: Of 38 studies identified, four could be used to evaluate rates of pain relief on a yearly basis, and two for actuarial rates of complete pain relief; seven provided data on latencies and 18 were used to evaluate complications.

Pain relief typically occurs within three months. Complete relief is initially achieved by three quarters of the patients, but half maintain this outcome at three years. One half or less can permanently stop drug treatments. Sensory disturbance, including anaesthesia dolorosa, is the most frequent complication of stereotactic radiosurgery.

Conclusions: Outcomes after stereotactic radiosurgery appear in line with other ablative techniques. Results are better when it is used as primary treatment in patients with typical symptoms. Current data are largely observational and the quality is generally poor. This technique should be evaluated in a randomised, controlled trial with universal outcome measures, actuarial methodology, and validated measures of patient satisfaction and quality of life.

The typically sudden, usually unilateral, severe, brief, stabbing, and recurrent pain of trigeminal neuralgia is initially managed medically. Increasing pain intensity and side effects from drug treatment make surgical options more effective. Unlike other chronic pain syndromes, patients with trigeminal neuralgia expect 100% pain relief outcome; off all drug treatment, for over five years after surgical treatment.

Current surgical treatments for trigeminal neuralgia can be classified into ablative and non-ablative. Generally, but not universally, it is accepted that the only non-ablative technique is neurovascular decompression. This appears to provide the best rates of long term complete pain relief and preservation of facial sensation. It is, however, a major neurosurgical procedure, with its attendant risks. Ablative techniques (radiofrequency thermocoagulation, glycerol rhizolysis, balloon compression, or posterior fossa partial sensory rhizotomy) employ physical or chemical methods in order to damage the trigeminal nerve at specific sites. With the exception of the partial sensory rhizotomy, ablative techniques are minimally invasive, require a short hospital stay, and provide immediate relief of pain in most patients. Their disadvantage is the comparatively high rate of facial sensory loss, trigeminal motor dysfunction, and pain recurrence. Stereotactic radiosurgery is an ablative procedure.

Since first developed in 1951 by Leksell, the initial problems with targeting the lesion and focusing the irradiation dose have been largely resolved by the development of magnetic resonance imaging (MRI) and the Gamma Knife®. The first multi-institutional study showed that the minimum radiosurgical dose that should be used for trigeminal neuralgia is 70 Gy, delivered to a 4 mm target at the sensory root of the trigeminal nerve. Subsequently it has been shown that the effects of radiosurgery are mediated through non-selective direct axonal damage with no vascular occlusion or thrombosis, and that the post-irradiation changes are established by six months post-treatment.

Increasing numbers of reports of different quality are being published about the results of stereotactic radiosurgery in trigeminal neuralgia. Patients, clinicians, and institutions responsible for funding do not currently have a clear picture of the results of the treatment, owing to the lack of uniformity of diagnostic criteria, outcome measures, treatment protocols, reported complications, and general quality of the literature. A review of all the neurosurgical literature on surgical management of trigeminal neuralgia has shown that the data are observational and the quality of reporting generally poor.

Our aims in this study were therefore, first, to evaluate systematically the published reports on radiosurgical management of trigeminal neuralgia against stringent quality criteria, so as to provide a summary of the best observational data available on its short term efficacy; and second, to provide recommendations for future higher quality reports.

METHODS

A comprehensive search of the literature was carried out since the start of electronic databases until the end of March 2003 using Medline, Embase, BIDS, and the Cochrane Library, as well as the references of reported studies. The search was also carried out by the editorial team of Clinical Evidence in preparation of an article on randomised controlled trials in the management of trigeminal neuralgia. The search strategy is available from the authors.

The appropriate studies were then evaluated for quality using 15 criteria set by a panel of 11 neurosurgeons and two
neurologists, all members of the US and UK trigeminal neuralgia associations advisory boards. The quality criteria were the data which the panel felt were essential in a study reporting outcomes of surgery for trigeminal neuralgia (table 1, item 1). All the identified studies were read and scored independently by two of us, blinded to the other’s findings (one point for each criterion present, up to a maximum of 15). The quality scores showed no inter-rater and intra-rater agreement ranging from 0.6 to 0.9. Studies needed to score 10 or higher to be considered. In addition, further inclusion criteria also had to be met, as shown in table 1, items 2 to 9. Individual case reports of unusual but potentially serious complications were used.

The main outcome measure for this study was the duration of complete pain relief on or off drug treatment as measured by actuarial methodology. Outcomes of the different studies were assessed to the point of median follow up of the series or to the next yearly milestone if follow up was between these times. Other outcome measures were times to complete pain relief, recurrence rates, and complications.

RESULTS
Study selection and patient population
The literature search yielded 38 studies. Twenty-six were rejected. Of these, eight were repeat studies or reviews not containing enough patient detail, five reported fewer than 30 patients, two dealt mostly with secondary trigeminal neuralgia, two reported results of repeat stereotactic radiosurgery for recurrent trigeminal neuralgia, five focused on imaging or other techniques, three had low scores as the inclusion criteria also had to be met, and, as shown in table 1, items 2 to 9. Individual case reports of unusual but potentially serious complications were used.

Four studies used actuarial methodology. Three high scoring studies using actuarial methodology could be used to evaluate pain outcomes, but only two provided data on complete pain relief. High scoring studies not using actuarial methodology could not be used for evaluation of pain outcomes but could be used for estimation of latency to pain relief.

The characteristics of the patient population and treatment protocols are given in table 2, and show considerable homogeneity in the selected studies.

All patients had primary trigeminal neuralgia. Sixteen of 220 (7.3%) in one study and eight of 117 (7%) in another series had atypical features—that is, dull aching constant background pain in addition to classical features of trigeminal neuralgia. All studies have a considerable proportion of patients who have had previous surgical procedures for their trigeminal neuralgia.

Pain outcomes
The maximal level of pain relief is typically achieved within one month of treatment (table 3). Disappearance of the trigger areas or frank pain relief occurs within 24 hours of treatment in up to one third of treated patients. Complete pain relief within one week of treatment is reported in over 40% of eventual responders. Over three quarters of partial and complete responders will have responded within three months of treatment, and over 90% of responses are seen by six months.

Complete pain relief on or off drug treatment is initially achieved by approximately three quarters of patients, but less than 60% maintain this outcome at two years, and just over half of the treated patients remain pain-free on or off drug treatment at three years (fig 1). Although two thirds of the treated patients are able to stop anticonvulsants at some point, one half or fewer remain off drug treatment and pain-free at the last follow up evaluation (table 4).

Approximately 15% of patients fail to obtain 50% pain relief. If treatment failure is defined as failure to obtain complete pain relief, the failure rate is doubled. Median time to pain recurrence is less than 12 months. When recurrence is defined as any deterioration from the maximum level of pain relief, the observed recurrence rates are 21%, at a median of 6.7 months (range 1 to 20), and 36% to 40% at two years (table 5).

Complications
Complications are shown in table 6. There are no reported deaths, systemic complications, or cases of radiosurgery induced malignancy following treatment of trigeminal neuralgia. The irradiation dose received by the lens of the eye during these procedures (7.7 ± 0.6 Gy) could induce cataracts in 0.1% of the patients, but this has not yet been reported.

Transient hearing loss, facial palsy, and permanent loss of taste have been described. Jaw clenching has been.
reported in one case following a larger than average dose (160 Gy).23

Asymptomatic vascular changes adjacent to the trigeminal nerve have been identified in patients who underwent neurovascular decompression for failed radiosurgery.24

New permanent numbness and dysesthesias are seen in 9–16% of the cases,13 15 18 19 although they are reported in more than half the patients treated with 90 Gy.20 Loss of the corneal reflex was seen in up to 10% of cases following administration of 80 Gy and 90 Gy,20 21 but keratitis or visual loss remains unreported to date.

Dysaesthesias affecting the quality of life are seen in 13% of patients treated with 90 Gy and 4% of those treated with 70 Gy.24 There are no reported cases of anaesthesia dolorosa as such. However, one study described a patient who developed touch precipitated pain in a numb area of the face15; another study described a patient who developed deafferentation pain eight months after stereotactic radiosurgery7; a further study reported a patient who developed severe dysaesthesias with increased numbness following 75 Gy stereotactic radiosurgery in two isocentres.13 This patient motivated the halting of recruitment into the two-isocentre limb of the trial.

Prognostic factors
All the studies meeting the required inclusion criteria have found lower recurrence rates in patients with typical pain who achieve complete relief off drug treatment and who undergo stereotactic radiosurgery as the primary treatment, with no previous ablative surgery. In this group Young et al found a recurrence rate of 3.3%,13 Maesawa et al 5%,21 and Pollock et al 7%.14 No recurrences were observed after 12 months, and two thirds of the treated patients in this group remained completely pain-free on or off drug treatment at three years (fig 1). One study found no differences with respect to previous surgery; however, it did not meet the inclusion criteria as 10% of the patients had multiple sclerosis, follow up was short, and it contained no data on failures and recurrences.28

Increasing the radiosurgical dose (from 70 Gy to 90 Gy) or the number of lesions (from one to two isocentres) has not produced an improvement in pain outcomes, but has caused a significant increase in the rate of sensory complications.14 20

Atypical features may be associated with a poorer response to treatment and a greater probability of pain recurrence.13 15 19 Rogers et al found complete pain relief rates of 49% in typical and 9% in atypical trigeminal neuralgia.19 In addition, the recurrence rate in patients who achieved complete pain relief off drug treatment was 4.5%, compared with 33% in those unable to stop pharmacological treatment. Maesawa et al found 84.4% pain relief (greater than 50%) at six months in typical cases of trigeminal neuralgia, v 43.8% in atypical cases.13 Pollock et al did not find differences in these groups.14

The development of new numbness has been found to correlate with sustained complete pain relief. Three quarters of patients with new numbness are free of pain and drug treatment at three years, compared with fewer than half of those with no new numbness.14 In a previous study, the same investigators found a 15% recurrence rate at 18 months if new numbness ensued, compared with 41% of recurrences at 12 months in the group with no new numbness.20

DISCUSSION
This systematic review shows that the results of stereotactic radiosurgery are comparable with those of other ablative techniques, and the best results are obtained in patients who have classical trigeminal neuralgia, for whom this is the first

<table>
<thead>
<tr>
<th>Table 2 Patient population included in outcome evaluations of pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Young et al, 199813</td>
</tr>
<tr>
<td>Maesawa et al, 200113</td>
</tr>
<tr>
<td>Pollock et al, 200124</td>
</tr>
<tr>
<td>Rogers et al, 200114</td>
</tr>
<tr>
<td>Pollock et al, 200120</td>
</tr>
<tr>
<td>90 Gy</td>
</tr>
<tr>
<td>Flickinger et al, 200118</td>
</tr>
<tr>
<td>Two isocentres</td>
</tr>
</tbody>
</table>

Studies 1 to 3 were included for actuarial evaluation of pain outcomes. Studies 2 and 3 provided data on rates of complete pain relief. All studies were used to evaluate postoperative trigeminal sensory complications.

*Percentage of patients who had undergone previous surgical treatments.

<table>
<thead>
<tr>
<th>Table 3 Latency to pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days to onset of pain relief</strong></td>
</tr>
<tr>
<td>Kontzios et al, 199916</td>
</tr>
<tr>
<td>Young et al, 199815</td>
</tr>
<tr>
<td>Maesawa et al, 200113</td>
</tr>
<tr>
<td>Pollock et al, 200124</td>
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<tr>
<td>Rogers et al, 200017</td>
</tr>
<tr>
<td>Friedman et al, 200121</td>
</tr>
<tr>
<td>Nicol et al, 200025</td>
</tr>
<tr>
<td>Urgoski et al, 199816</td>
</tr>
<tr>
<td>Zheng et al, 200117</td>
</tr>
</tbody>
</table>

Values are median (range). NS, not stated.
surgical treatment and who develop postoperative numbness. Typically, the maximal level of pain relief after radiosurgery is achieved within one month. The histological effects of radiosurgery and the reported latencies indicate that it is safe to consider the treatment a failure if no response has taken place after three to six months. Recurrences are commonest in the first year. Like other ablative techniques, stereotactic radiosurgery does not preserve trigeminal function.

When standard criteria for the evaluation of randomised controlled trials are applied to the observational data available, the deficiencies of the evidence in this field become obvious. Inconsistencies in defining the diagnostic criteria and outcome measures and the infrequent use of actuarial methodology for the evaluation of results make most studies methodologically unsuitable from an evidence based viewpoint. This phenomenon is common to all techniques.10

Excellent results (no pain and no drug treatment) are seldom reported separately, and patients with complete relief are often pooled with patients with partial relief. What is a treatment failure, what is deemed a recurrence, and what definitions are being used for postoperative changes in sensation are often not considered or incompletely defined.

Although most studies have carried out follow up at least partly by telephone or mail interview, no study provides the actual questionnaire. Consequently, although the level of pain relief has been measured postoperatively, it is not known whether the same measures have been universally applied, as the questions put to the patients may have varied considerably. As a result, data on partial relief cannot be directly compared across current studies. In addition, although the median follow up for the selected studies was at least 12 months, the ranges show that patients followed up for as short a time as two months have been included in the results, whereas the time to response can extend to six months and the median time to recurrence with this technique appears to be six to nine months. Future studies should ensure that all patients have been followed up for at least 12 months.

Some studies claim to report long term outcomes, yet the median follow up of all series is less than three years. As the results of Kaplan–Meier survival plots are valid up to the median time of follow up,13 one must conclude that no published reports of methodologically sound long term data are currently available for this technique.

In spite of the above limitations, the results in the studies using stringent methodology13 14 are remarkably consistent and show that initially over two thirds of treated patients will obtain complete pain relief with this technique. A further 10–15% of patients experience a partial reduction in the severity and frequency of the attacks and are able to reduce their drug treatment,15 but fewer than half of the treated patients are able to stop all drug treatment permanently. This may make it less suitable for patients who opt for surgery because of drug intolerance.

Percutaneous techniques, such as radiofrequency thermocoagulation, glycerol rhizolysis, and balloon compression, seem to offer higher rates of early complete pain relief than stereotactic radiosurgery.29–35 However, excluding facial sensory loss, approximately one quarter of patients treated with radiofrequency thermocoagulation or glycerol rhizolysis will experience some transient or permanent complication, compared with 10% or less of the patients treated with stereotactic radiosurgery.36–39

Permanent facial sensory loss affects two thirds of the patients treated with radiofrequency thermocoagulation,39 and 25% of the patients consider it has had a long term detrimental effect on their quality of life.39 When less than 90 Gy is used, permanent sensory loss is seen in approximately 15% of patients treated with stereotactic radiosurgery, and at the higher dose of 90 Gy, 13% of patients experience sensory disturbances interfering with their quality of life.39 Masseter weakness, rare with radiosurgery, can cause long term mastication disturbances in 10% or more of the patients after balloon compression and radiofrequency thermocoagulation.39–40 Meningitis and neurovascular injury are infrequent but serious complications of percutaneous techniques.39–41

Although rare, mortality has been described with all percutaneous techniques.39–41

Although reported as “severe dysesthesias,” these investigators contend that the descriptions of at least one of the

### Table 4 Failures and recurrences

<table>
<thead>
<tr>
<th></th>
<th>Ever off drug treatment</th>
<th>Remain off drug treatment</th>
<th>Initial failures</th>
<th>Recurrence</th>
<th>Months to recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al, 1998</td>
<td>NS</td>
<td>NS</td>
<td>12%</td>
<td>34%</td>
<td>25 to 33 [mean]†</td>
</tr>
<tr>
<td>Maesawa et al, 2001</td>
<td>47.7%</td>
<td>40%</td>
<td>15%</td>
<td>16.6%</td>
<td>15.4 [mean]‡</td>
</tr>
<tr>
<td>Pollock et al, 2002</td>
<td>59%</td>
<td>50%</td>
<td>14%</td>
<td>20%</td>
<td>5 to 8 [median]‡</td>
</tr>
<tr>
<td>Rogers et al, 2001</td>
<td>41%</td>
<td>39%</td>
<td>11%</td>
<td>21% (36%)*</td>
<td>6.7 [median]‡</td>
</tr>
<tr>
<td>Pollock et al, 2002</td>
<td>70 Gy</td>
<td>56%</td>
<td>15%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>Flickinger et al, 2001</td>
<td>90 Gy</td>
<td>59%</td>
<td>7%</td>
<td>16%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>One isocentre</td>
<td>54.5%</td>
<td>16%</td>
<td>41.6%</td>
<td>12 [median]</td>
</tr>
<tr>
<td></td>
<td>Two isocentres</td>
<td>49%</td>
<td>18.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentages of patients able to stop drug treatment, rates of recurrence of the different series, and times to recurrence.

*The authors report a crude recurrence rate of 21% (11 of 52 patients) but an actuarial recurrence rate of 36% the patients followed up for 2.5 years.
†Mean time to recurrence 25 months in patients with previous surgery and 33 in those with no previous surgery.
‡Median time to recurrence = 5 months in patients requiring drug treatment and 8 months in those previously pain-free off drug treatment.
NS, not stated in the study.

### Table 5 Actuarial rates of complete pain relief (data for fig 1)

<table>
<thead>
<tr>
<th></th>
<th>3 months (%)</th>
<th>6 months (%)</th>
<th>12 months (%)</th>
<th>24 months (%)</th>
<th>36 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>No Sx</td>
<td>Sx</td>
<td>All</td>
<td>No Sx</td>
</tr>
<tr>
<td>Maesawa et al, 2001</td>
<td>72</td>
<td>75</td>
<td>70</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>Pollock et al, 2002</td>
<td>68</td>
<td>74</td>
<td>61</td>
<td>66</td>
<td>72</td>
</tr>
</tbody>
</table>

All, all treated patients; no SX, patients who did not undergo any surgical procedures before radiosurgery; SX, patients who underwent previous surgical procedures.
patients whose radiosurgical treatment was complicated by “severe deafferentation pain” describe anaesthesia dolorosa, which can occur with this technique as it can with other ablative techniques.13 18

These data suggest that, currently, stereotactic radiosurgery is the safest technique for the treatment of trigeminal neuralgia, although probably not the most effective. In practice, trigeminal sensory disturbance is the main radiosurgical complication. The rate of corneal numbness is approximately 10%,20 21 but keratitis remains unreported.

In a separate study, the investigators analysed the quality of reporting in all published reports on the surgical management of trigeminal neuralgia since the start of electronic databases, and suggested a set of recommendations about what data should be included and how they should be analysed.22 These include defining the diagnostic criteria, employing universal outcome measures, and improving the quality of follow up by using independent assessors and standardised questionnaires. In addition, Kaplan–Meier actuarial methodology must be adopted as the standard method for reporting results, and the exact number of patient selection and facilitate future trials.

Quality of life may improve postoperatively even if incomplete pain control is attained. If studies are reporting less than 100% relief of pain then it is essential to have some objective means of measuring the pain and comparing it with a baseline measurement. In order to improve the quality of data, more than one outcome measure should be used, and quality of life assessments should be included.

Cost estimations would be useful for health care providers who are responsible for the funding of this technique, which may be considerably more expensive than percutaneous procedures and does not appear to offer better rates of early or mid-term pain control.

Our study summarises the best data currently available and highlights the need to report outcomes for longer than five years. Based on the findings from this review it is important that future studies address some of the identified shortfalls of the present data. Patients and clinicians need high quality data to evaluate the role of stereotactic surgery in the long term management of trigeminal neuralgia. It will improve patient selection and facilitate future trials.

Conclusions

Stereotactic radiosurgery is the least invasive current surgical treatment for trigeminal neuralgia. Its early results, in terms of rates of pain control and pain recurrence, appear to be in line with other ablative techniques. A history of no previous surgical procedures, typical symptoms, and the development of postoperative numbness may be associated with better pain outcomes.

Data on radiosurgical management of trigeminal neuralgia are largely observational and generally of poor quality. It is essential that the efficacy of this technique be evaluated in a randomised controlled trial with universal outcome measures, actuarial methodology, and appropriate assessments of patient satisfaction and quality of life.

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Competing interests: none declared

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