Fifteen years of Gamma Knife surgery for trigeminal neuralgia in the *Journal of Neurosurgery*: history of a revolution in functional neurosurgery

**Editorial**

**JEAN RÉGIS, M.D., AND CONSTANTIN TULEASCA, M.D.**

Functional and Stereotactic Neurosurgery Department, Aix-Marseille Univ, and Timone University Hospital, Marseille, France

(DOI: 10.3171/2011.12.GKSeditorial)

---

**Reappraisal of a Dated Idea**

In 1994 the Leksell Gamma Knife Society, under the presidency of Prof. Kintomo Takakura, held its meeting in Kyoto, Japan. I presented 5 cases of trigeminal neuralgia that had been successfully treated using the Gamma Knife at a dose of 90 Gy and an anterior cisternal target (retrogasserian target). My presentation was very well attended and raised a great deal of interest because of its “novelty”! In fact, 37 years earlier, the first radiosurgical procedure in a human had been performed by Lars Leksell to treat trigeminal neuralgia by targeting the gasserian ganglion as seen on x-ray films. After treating a series of 40 patients, the Leksell team abandoned this approach because Lars Leksell discovered the efficacy of the glycerol injection. This injection was first used for visualization of the Meckel cave but turned out to be sufficient to stop pain in a significant percentage of patients. The clear limitations of other medical and surgical therapeutic options, on the one hand, and the possibility of accurate direct targeting of the cisternal portion of the nerve, on the other hand, explains the revival of the idea of radiosurgery for tic douloureux in the early 1990s.

**A Seminal Multicentric Study**

Doug Kondziolka came to me with a short series of patients who had been treated less successfully in Pittsburgh using a lower dose of radiation. He proposed that we combine our two series for a publication demonstrating the dose effect in treating trigeminal neuralgia. Some months later, after we had added more cases from Rhode Island and Seattle, we were able to publish, in the *Journal of Neurosurgery (JNS)*, what is now considered a seminal paper demonstrating for the first time the safety efficacy of GKS at maximum doses between 70 and 90 Gy. That paper initiated a profound change in radiosurgical practice, which rapidly translated into more patients undergoing radiosurgery (Fig. 1) and a large number of papers documenting its safety efficacy (Figs. 2–4). Interestingly, many key papers were also published in *JNS* (Fig. 4).

**The Major Contribution of JNS to the Establishment of Gamma Knife Surgery**

This supplement contains the 25 most frequently cited articles in *JNS* on GKS for trigeminal neuralgia according to a recent search of Web of Science. The majority of these “Top 25” papers have made great scientific contributions to the field. Soon after the multinstitutional study was published in 1996, good short-term safety efficacy of GKS was confirmed by three studies of large cohorts of patients treated using the so-called DREZ target (site of the dorsal root entry zone). These papers established better long-term results in patients who had not previously undergone surgery. However, globally, papers in the literature frequently report results based on very heterogeneous methodologies. Because the effect of radiosurgery is delayed, efficacy can be appreciated very differently if authors report only initial pain cessation, with or without medication, rather than long-term freedom from pain without medication (Table 1). Sometimes

*Abbreviations used in this paper: DREZ = dorsal root entry zone; GKS = Gamma Knife surgery; JNS = Journal of Neurosurgery; MVD = microvascular decompression.*
patients who no longer feel pain are mixed with patients who have more than a 90% reduction in the number of pain attacks! We consider it mandatory to report patients who are free from pain, with or without medication, separately from patients whose pain has improved but has not completely ceased. Additionally, rates of recurrence after surgery (whatever the approach) are significant, and authors must report Kaplan-Meier rates of pain freedom at 1, 2, 3, or more years instead of freedom from pain at the last follow-up. The only prospective trial published to date was one published in JNS by our group in 2006.29 That paper fulfills all the major criteria for “quality reporting in surgery for trigeminal neuralgia,” specified by Zakrzewska in 2003,34 with the exception of minimum follow-up, which was 1 year in the paper.

Nuances in Technique Make Significant Differences in Clinical Results

In the early 1990s, thanks to magnetic resonance imaging, Rand24 proposed to move the radiosurgical target from the ganglion to the cisternal segment of the nerve.
Christer Lindquist then promoted the elegant idea of targeting the DREZ by directing a 4-mm shot at the site where the trigeminal nerve emerges from the pons and by overlapping generously the adjacent brainstem. Because the site where the myelin sheath of peripheral sensory nerves shifts from a composition of Schwann cells to one of oligodendrocytes is a classic target in pain surgery, this idea made a lot of sense and became very popular. However,
TABLE 1: Clinical results reported in 17 papers on series of patients with typical trigeminal neuralgia*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Mean Age in Yrs (range)</th>
<th>Median FU in Mos (range)</th>
<th>% Pts Pain Free at</th>
<th>% Pts w/ Improvement &gt;90%†</th>
<th>% Pts w/ SE (CN V Dist)</th>
<th>INP</th>
<th>% Pts w/ Recur</th>
<th>Shot Location (mm)</th>
<th>% Pts w/ Max Dose</th>
<th>% Pts w/ 2 Isocenters</th>
<th>Zakrzewska</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kondziolka et al., 1996</td>
<td>50</td>
<td>70</td>
<td>18</td>
<td>58</td>
<td>94</td>
<td>6</td>
<td>6</td>
<td>2–4</td>
<td>11</td>
<td>29</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Maesawa et al., 2001</td>
<td>220</td>
<td>70</td>
<td>24 (6–78)</td>
<td>40.0</td>
<td>63.6</td>
<td>56.6</td>
<td>40</td>
<td>69.1</td>
<td>0.4–10.2</td>
<td>13.6</td>
<td>2–4</td>
<td>2.7</td>
</tr>
<tr>
<td>Pollock et al., 2002</td>
<td>117</td>
<td>67.8</td>
<td>26 (1–48)</td>
<td>59</td>
<td>57</td>
<td>55</td>
<td>85</td>
<td>37, 12–25</td>
<td>16</td>
<td>5.9</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>Nicol et al., 2000</td>
<td>42</td>
<td>14 (2–30)</td>
<td>73.8</td>
<td>21.4</td>
<td>26.2</td>
<td>10 (REZ)</td>
<td>0</td>
<td>0 no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Régis et al., 2006</td>
<td>110</td>
<td>68.2</td>
<td>&gt;12</td>
<td>83</td>
<td>97</td>
<td>10, 5–5</td>
<td>17</td>
<td>7.84</td>
<td>0</td>
<td>85 Gy (70–90 Gy)‡</td>
<td>0</td>
<td>yes</td>
</tr>
<tr>
<td>Brisman et al., 2000</td>
<td>172</td>
<td>56.5/65.11§</td>
<td>6 &amp; 12</td>
<td>89.8/71.4$</td>
<td>0–2</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0 no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheehan et al., 2005</td>
<td>151</td>
<td>68 (22–90)</td>
<td>19 (2–96)</td>
<td>44</td>
<td>47</td>
<td>34</td>
<td>44</td>
<td>90</td>
<td>19</td>
<td>24</td>
<td>2–4</td>
<td>1.4</td>
</tr>
<tr>
<td>Massager et al., 2004</td>
<td>47</td>
<td>69</td>
<td>16 (6–42)</td>
<td>59</td>
<td>75</td>
<td>59</td>
<td>83</td>
<td>71</td>
<td>38, bo in 4</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Tawk et al., 2005</td>
<td>38</td>
<td>70 (29–88)</td>
<td>24 (6–27)</td>
<td>44</td>
<td>70</td>
<td>37</td>
<td>REZ</td>
<td>0</td>
<td>60</td>
<td>39</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Matsuda et al., 2002</td>
<td>41</td>
<td>13 (3–36)</td>
<td>60</td>
<td>100</td>
<td>17.1, dry eye in 7.3</td>
<td>7.3</td>
<td>~0</td>
<td>0</td>
<td>41</td>
<td>0</td>
<td>0 no</td>
<td></td>
</tr>
<tr>
<td>Urgosik et al., 2005</td>
<td>107</td>
<td>75 (45–91)</td>
<td>60 (12–96)</td>
<td>80</td>
<td>96.3</td>
<td>20</td>
<td>25.0</td>
<td>REZ</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0 no</td>
</tr>
<tr>
<td>Dhople et al., 2010</td>
<td>503</td>
<td>72 (26–95)</td>
<td>24 (3–156)</td>
<td>89</td>
<td>80</td>
<td>71</td>
<td>46</td>
<td>29</td>
<td>10.5</td>
<td>0.2</td>
<td>43</td>
<td>3–8</td>
</tr>
<tr>
<td>Sekula et al., 2009</td>
<td>112</td>
<td>64 (24–96)</td>
<td>5.6 (13–115)</td>
<td>81</td>
<td>60</td>
<td>41</td>
<td>34</td>
<td>91</td>
<td>6</td>
<td>0</td>
<td>28</td>
<td>REZ</td>
</tr>
<tr>
<td>Balamucki et al., 2006</td>
<td>239</td>
<td>65 (22–90)</td>
<td>17 (0.7–59)</td>
<td>55.8</td>
<td>79.7</td>
<td>23</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 no</td>
</tr>
<tr>
<td>Alpert et al., 2005</td>
<td>63</td>
<td>56 (19–84)</td>
<td>10 (3–63)</td>
<td>27</td>
<td>90</td>
<td>7.93</td>
<td>0</td>
<td>15.67</td>
<td>REZ</td>
<td>0</td>
<td>20</td>
<td>43</td>
</tr>
</tbody>
</table>

* bo = bothersome; INP = iatrogenic neuropathic pain; FU = follow-up; Pts = patients; Recur = recurrence; REZ = root entry zone; SE (CN V Dist) = side effects (trigeminal nerve disturbance); Shot Location = location of the shot from the emergence of the nerve from the brainstem; Zakrzewska = series in which at least 10 of the 12 major criteria for quality reporting in trigeminal neuralgia surgery have been fulfilled.
† Percentage of patients who are free from pain or experienced a reduction in pain frequency that was > 90%.
‡ Information on dosing provided in text.
§ Article contains 2 groups: patients who underwent GKS as the first neurosurgical intervention and patients who had undergone previous neurosurgical procedures, respectively.
in our group we were concerned about the potential risk of brainstem injury, which led us to propose a more anterior target, 7–8 mm anterior to the emergence of the nerve from the pons, coined the “retrogasserian target.”15,18 In the prospective trial the safety efficacy of the procedure using an average dose of 85 Gy and a retrogasserian target compared favorably to that of a series in which the radiation dose was lower and the target the DREZ.29 The potential benefit of these technical nuances to avoid source shielding,19 which can lead to an increased rate of hypesthesia according to the “Flickinger effect,” has been confirmed by several other papers in the Top 25.15,18 In a comparison of one-shot and two-shot strategies, John Flickinger and the Pittsburgh team demonstrated that increasing the volume of the fifth cranial nerve that is treated leads to a dramatic increase in the risk of toxicity with no clear benefit in efficacy.6 Brisman and Pollock and colleagues showed that the use of a low dose (75 Gy) on the DREZ target requires being more aggressive to the brainstem in order to achieve good short-term efficacy.3,19,21,25 Consequently, maximum dose, volume of nerve treated, and anatomical location of the target (and hence the dose to the intraxial portion of fifth nerve fibers in the brainstem) are technical nuances of radiosurgery that have a major impact on both the probability of long-term pain control and the probability and severity of fifth cranial nerve disturbance.

Defining the Limits

Our group28 and that of Chang4 reported high rates of pain relief in patients who underwent radiosurgery for secondary trigeminal neuralgia. The safety efficacy of a second radiosurgical treatment was reported in 2000 by Pollock and colleagues20 and again in 2002 by Shetter et al.32 According to the former group, much better efficacy is associated with the first radiosurgical intervention.20 Atypical trigeminal neuralgia, not surprisingly, has been described to respond less favorably to radiosurgery, with both a lower chance of satisfactory pain relief and a greater risk of worsening a neuropathic mode.2,3,35

The Least-Invasive Surgical Technique for Tic Douloureux

The only complication reported in these papers was a more-or-less disabling disturbance in trigeminal nerve function, including dry eye in the 2002 study by Mutsuda et al.17 An “evidence-based” review of the literature published in Neurology by the Federation of Neurological Societies clearly established that in the literature the rate of hypesthesia following MVD is not significantly different from that after GKS, although the rate is much lower than the one associated with percutaneous treatments.7 Other complications (cerebellar lesion, CSF leak, aseptic or bacterial meningitis, diplolia, deafness, facial palsy, and others) associated with MVD and/or percutaneous treatments have not been reported following radiosurgery.7

Hypesthesia is Not Necessary for a Long-Lasting Effect!

Clearly the small subgroup of patients with hypesthesia has a higher probability of long-lasting pain relief,19 but what is more important is that the vast majority of patients experiencing long-term pain control do not experience any kind of trigeminal nerve dysfunction.5,11,29 Contrary to destructive techniques of treating trigeminal neuralgia, such as thermocoagulation, balloon microcompression, and glycerol injection, with radiosurgery hyposthesia is not mandatory for durable efficacy.

Long-Term Safety Efficacy

Importantly, Dhople et al.5 and Kondziolka and colleagues11 reported their long-term results (> 100 patients with a follow-up > 5 years for Kondziolka’s series). Using the DREZ as the target with quite low radiation doses, both teams reported a steady rate of late failure: for Dhople et al. 22% of patients remained pain free at 7 years, and for Kondziolka and colleagues 30% of patients at 10 years had Barrow Neurological Institute Scale Scores I through IIIb.31 Long-term results with high radiation doses and the anterior cistern as the target have not yet been published.

Microvascular Decompression

Microvascular decompression remains the reference technique for the majority of authors, despite the fact that in the absence of a serious prospective randomized comparative trial (with a sufficiently large population and lengthy follow-up) no definitive statement can be made concerning the superiority of one technique over the other. However, if both MVD and GKS have very significant rates of long-term recurrences, the probability of being pain free without medication looks better in the MVD group,21,23 The majority of authors who have at their disposal the technical and human resources allowing them to offer MVD, GKS, and percutaneous techniques agree that the current evidence for the long-term safety efficacy of GKS is sufficient to propose GKS as the first intervention.5,9,11,29 Advantages and disadvantages of each technique must be disclosed to the patient, as advocated in modern serious peer-reviewed series published in the last 16 years.

In conclusion, this series of the Top 25 papers in JNS on GKS for trigeminal neuralgia bears witness to the fact that radiosurgery is an example of a true disruptive innovation in the field of functional neurosurgery and, specifically, in the neurosurgical management of trigeminal neuralgia. These articles demonstrate how greatly this innovation has changed neurosurgical practice in just a few years.

Disclosure

Professor Régis states that, although he receives no money personally, his institution received money for research from Elekta AB, and the scientific society for which he is president, the International Stereotactic Radiosurgery Society (ISRS), received significant sponsorship from Elekta for its last meeting. Dr. Tuleasca states he has no conflict of interest.

References

Editorial

2. Brisman R: Gamma knife surgery with a dose of 75 to 76.8 Gray for trigeminal neuralgia. J Neurosurg 100:848–854, 2004

Address correspondence to: Jean Régis, M.D., Timone University Hospital, Functional Neurosurgery, 264 Bvd St. Pierre, 13385 Cedex 05, Marseille, France. email: jregis@ap-hm.fr.