Bibliometric Analysis of the Top 100 Cited Articles on Stereotactic Radiosurgery for Trigeminal Neuralgia

Parth Parikh[1,*] Hussein M. Abdallah[2,*] Aneek Patel[3] Rimsha K. Shariff[4] Kamil W. Nowicki[4] Arka N. Mallela[4] Daniel A. Tonetti[5] Raymond F. Sekula Jr.[6,7] L. Dade Lunsford[4] Hussam Abou-Al-Shaar[4]

[1] Mayo Clinic Alix School of Medicine, Scottsdale, Arizona, United States
[2] University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States
[3] New York University School of Medicine, New York, New York, United States
[4] Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States
[5] Cooper Neurological Institute, Cooper Medical School of Rowan University, Camden, New Jersey, United States
[6] Department of Neurological Surgery, Columbia University Medical Center, New York, New York, United States
[7] Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, United States

Address for correspondence Hussam Abou-Al-Shaar, MD, Department of Neurological Surgery, University of Pittsburgh Medical Center, 200 Lothrop Street, Suite B-400, Pittsburgh, PA 15213, United States (e-mail: aboualshaarh@upmc.edu).

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Abstract

Background Stereotactic radiosurgical rhizolysis of the trigeminal nerve is an established modality increasingly employed to alleviate the symptoms of refractory trigeminal neuralgia. This study analyzes the academic impact of the top 100 cited articles on the radiosurgical management of trigeminal neuralgia.

Methods The Scopus database was searched for articles containing “radiosurgery” and one or more of “trigeminal neuralgia,” “trigeminus neuralgia,” and “tic douloureux.” The top 100 articles written in English were arranged in descending order by citation count. Documents were evaluated for authors, publication year, journal and impact factor, total citations, nationality, study type, radiosurgical modality, and the affiliated institution. Quantitative and qualitative analyses were performed on the data.

Results The most cited articles were published between 1971 and 2019. The average citation per year was 4.3. The most targeted anatomic area was the “root entry zone” or proximal portion of the cisternal segment of the trigeminal nerve. The most utilized modality was Gamma Knife radiosurgery. The country with the highest number of publications was the United States. Thirty-six percent of the articles were published in the *Journal of Neurosurgery*. Lunsford, Kondziolka, Flickinger, and Régis, respectively, were the most frequently listed co-authors. The most prolific institute was the University of Pittsburgh Medical Center.

Keywords
- trigeminal neuralgia
- tic douloureux
- stereotactic radiosurgery
- Gamma Knife
- LINAC
- CyberKnife
- bibliometric analysis

* *The authors contributed equally and retain the first authorship.*

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Conclusion Stereotactic radiosurgery is an important modality in the management of medically or surgically refractory trigeminal neuralgia. This analysis assesses its contributions over the past five decades to identify trends in treatment practices for neurosurgeons and to highlight areas where further study is needed.

Introduction

Trigeminal neuralgia (TN) is a debilitating neuropathy with an incidence of less than 0.1% in the population.[1] It typically presents with paroxysmal episodes of lancinating facial pain; episodes are typically unilateral and triggered by light tactile stimulation.[1] Classical TN is most often associated with neurovascular compression of the cisternal segment of the trigeminal nerve.[2–5] Demyelination secondary to neurovascular compression of the cisternal segment of the trigeminal nerve with resultant hyperexcitability of the trigeminal ganglion is thought to play a role in the etiopathogenesis of classical TN.[6] Newer preclinical data suggest that dysregulation of voltage-gated sodium channels is also involved in the etiopathogenesis of the disease.[7] Less common secondary causes of demyelination, occurring in 15% of cases, include multiple sclerosis and structural brainstem lesions (such as cerebellopontine tumors and arteriovenous malformations). In approximately 10% of cases, the cause remains idiopathic.[8] Virtually all cases are sporadic and risk factors include older age and female sex.[9] Typically, painful periods lengthen, and pain severity worsens over time.

Multimodal treatment options are available for TN and usually begin with antiseizure drugs. Oral carbamazepine or oxcarbazepine are the most-studied agents, but additional medical options include gabapentin, phenytoin, baclofen, and more recently lamotrigine.[10,11] Medically refractory TN can be managed with microvascular decompressive or nerve ablative procedures including percutaneous trigeminal rhizotomy and stereotactic radiosurgery (SRS), each with its inherent advantages and limitations.[12–15] Sir William Horsley first described a surgical procedure for the treatment of TN in the late 19th century.[16] In the early 20th century, Walter Dandy proposed neurovascular compression as an etiology of TN.[17] Gardner advocated for decompression without injury of the proximal cisternal segment of the trigeminal nerve which in turn led Janetta to propose microvascular decompression as a procedure that addresses the cause of TN in many patients[12,18] The use of SRS for TN was first reported by Leksell et al in 1971.[19] Since then, it has become one of the most widely-utilized treatments for medically-refractory TN in part because of its minimal invasiveness, safety, efficacy, and ability to be performed as an outpatient procedure.[20]

A bibliometric analysis of the most cited articles in a field is a well-established method for highlighting the most significant publications in that particular field by assessing the scholarship of the work through the number of times it has been cited in other peer-reviewed articles.[21] The number of citations also lends insight into specific topics within the field that are actively being discussed as well as gaps in active scholarship. The goal of this study is to report the 100 most-cited articles on SRS management of TN with the intent of characterizing trends in literature over time and providing a landscape-level view of research regarding its clinical application.

Methods

The Scopus database was accessed in November 2021 and searched for articles with titles, abstracts, and keywords containing "radiosurgery" and one or more of "trigeminal neuralgia," "trigeminus neuralgia," and "tic douloureux." The top 100 articles published in journals were arranged in descending order by total citation count (CC). Exclusion criteria included articles that contained other conditions, were non-English articles, and articles that did not primarily focus on SRS for TN as the primary treatment modality or was one among several compared modalities.

After the final list was generated, each article on the list was analyzed by investigators for the following parameters of the bibliometric analysis: article title, author list, publication year, country of origin, the institution of the study (or primary institution), publishing journal, impact factor of the journal, type of study/article, the specific type of SRS modality if specified (including Gamma Knife [Elektra AB, Stockholm, Sweden], CyberKnife [Accuray, Sunnyvale, CA], or another linear accelerator [LINAC]), anatomical site that was targeted by the therapy, and total citation count. A "citations-per-year" value was assigned for each paper on the list by dividing the total citation number by the years elapsed since publication. The impact factor was calculated based on real-time 2022 values.

Results

A query of the Scopus database with the aforementioned criteria for inclusion and exclusion yielded 1,172 articles discussing SRS management of TN, from which the top 100 most highly-cited articles were selected (►**Supplementary Table S1**; available in the online version only). The top 100 articles discussing SRS management of TN were published between 1971 and 2019 (►**Fig. 1**). Seventy percent of the articles were published between 2000 and 2010. The highest number of articles were published in 2005 (10 articles), and the article with the highest citation count was published in 2000 (343 CC). The one hundred articles analyzed in this study garnered a total of 6,971 citations. The average citations-per-year across all the papers was 4.3. Eighty-nine percent of the articles in this list discussed the use of Gamma Knife radiosurgery for the management of TN, 4% reported the use of CyberKnife, 3% discussed LINAC broadly, and one

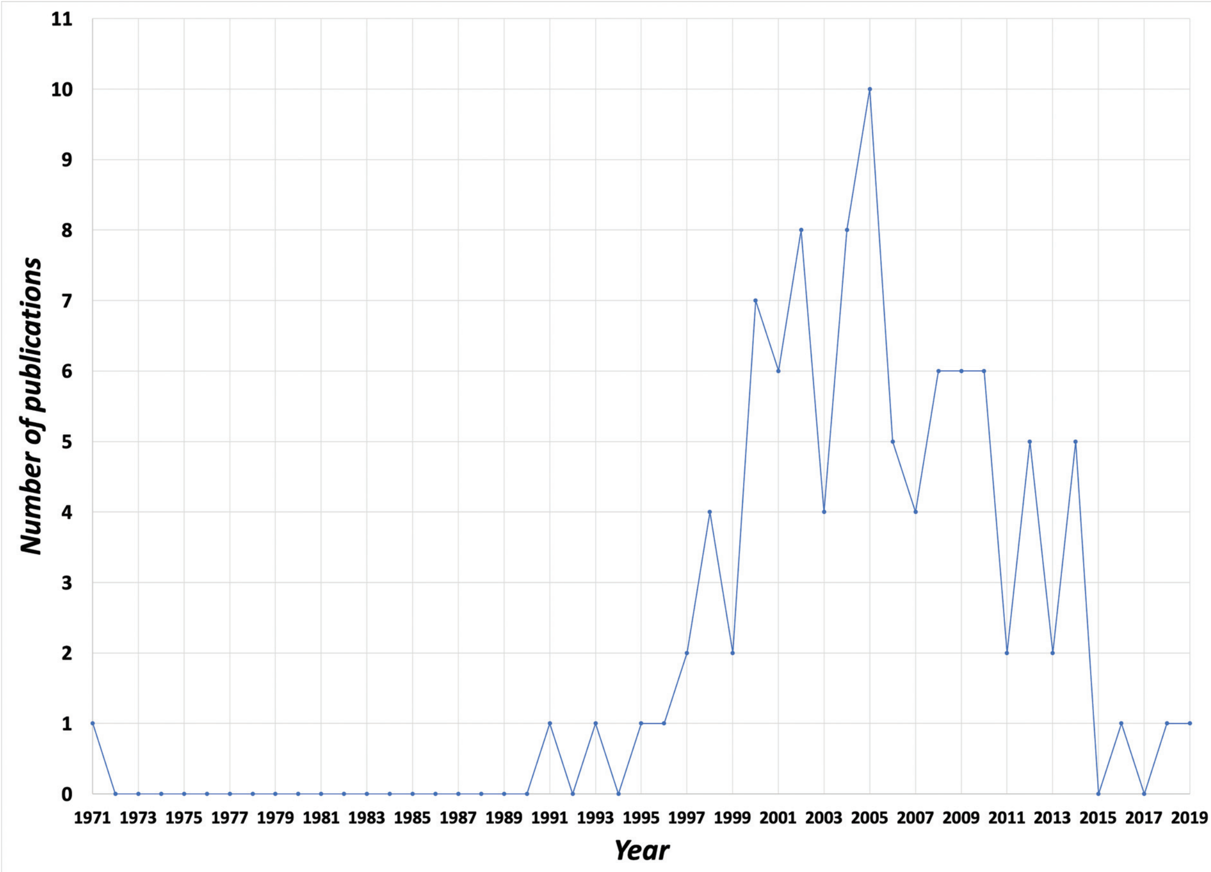

Fig. 1 Publication trends for the top 100 most cited articles on the stereotactic radiosurgical management of trigeminal neuralgia (1971–2019).

paper studied Novalis radiosurgery. One report discussed GKRS, LINAC, and CyberKnife together. Two articles did not discuss or advocate for a specific SRS technology (►**Fig. 2**). Ninety percent of the articles were case series, 3% were meta-analyses, 2% were translational studies, 2% were reviews; there was one individual case report (the very first report by Leksell), one prospective comparative study comparing microvascular decompression and GKRS in a single institution, and one prospective, double-blind randomized study.

The United States had the highest number of publications among this list of articles discussing SRS management of TN ($n = 70$), followed by France ($n = 8$), and Korea ($n = 4$), respectively (►**Fig. 3**). The United States also had the highest number of citations among the other countries and the most citations per year, followed by France. The University of Pittsburgh Medical Center in Pennsylvania, United States, was the most prolific institution, contributing 14% of the articles on this list. This was followed by Timone University in Marseille, France with seven publications, and Mayo Clinic in Minnesota, United States with six articles (►**Fig. 4**). The individuals who co-authored the most articles on this list were Lunsford, Kondziolka, Flickinger, Régis, Pollock, Foote, and Stafford, respectively (►**Fig. 5**).

The *Journal of Neurosurgery* (2022 impact factor: 5.1) was the journal that published the highest number of publications in the top 100 with 36% of the papers in this study. This was followed by *Neurosurgery* (2022 impact factor: 5.3)

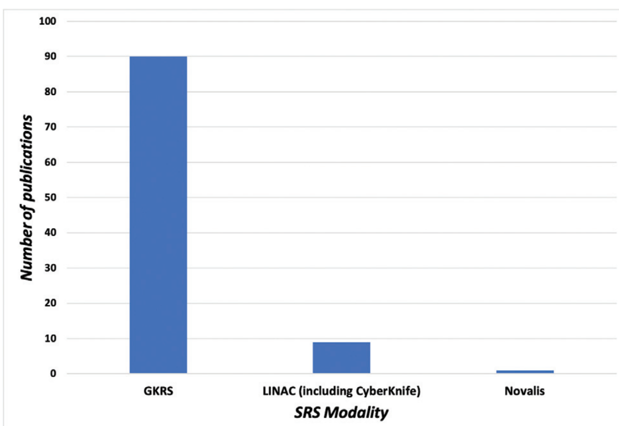

Fig. 2 Categorical distribution of different stereotactic radiosurgical modalities in the top 100 cited articles. SRS, stereotactic radiosurgery.

with 18% of papers (►**Fig. 6**). The article with the highest overall citation count was “Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute,” by Rogers et al[22] in 2000, published in the International *Journal of Radiation Oncology Biology Physics* with 343 citations. “Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study” by Régis et al[23] was the article that had the most citations-per-year with 15.7.

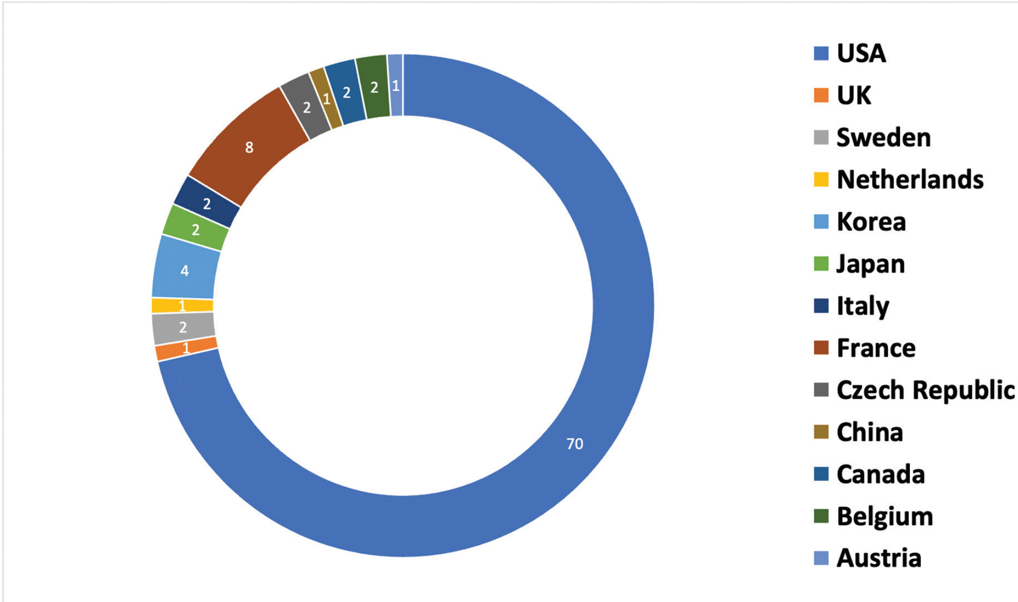

Fig. 3 Top countries generating articles in the top 100 cited articles on stereotactic radiosurgical management of trigeminal neuralgia based on the first author.

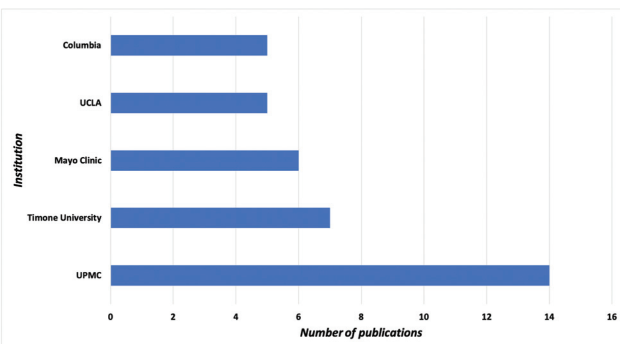

Fig. 4 Top contributing academic institutions in the top 100 cited articles. UCLA, University of California, Los Angeles; UPMC, University of Pittsburgh Medical Center.

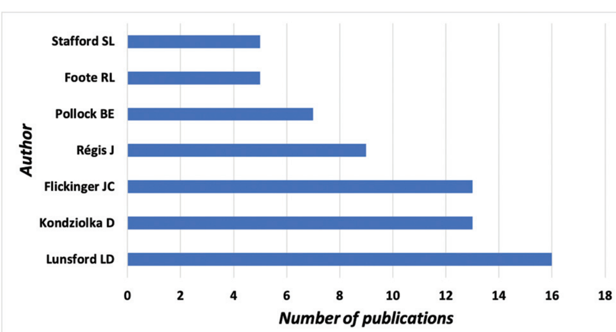

Fig. 5 Top contributing authors in the list of the top 100 cited articles.

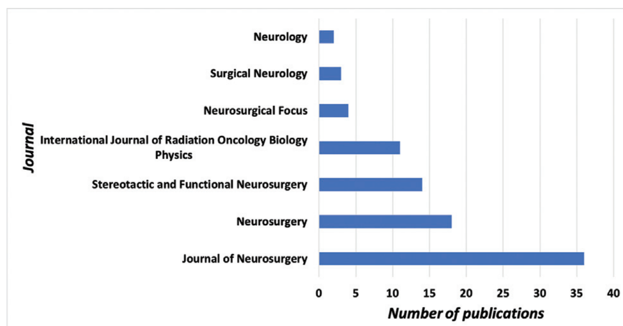

Fig. 6 Top contributing journals in the list of the top 100 cited articles.

Forty-five articles specified the target site of SRS for TN. Among these target sites, the root entry zone of the trigeminal nerve (also called the Obersteiner-Redlich zone)—the proximal point at which peripheral myelination transitions to central myelination—was the most-described specific treatment target site ($n = 25$).[24] The other common SRS target was the retrogasserian or distal target ($n = 7$), and the least common was the Gasserian ganglion itself (►**Fig. 7**). There was no appreciable trend between the year of publication and the anatomic site targeted by the specific SRS modality.

Discussion

TN is a debilitating condition that has seen several treatment modality developments in recent decades. With the advent of SRS for this condition in 1971 by Leksell,[19] SRS has been widely used for medically-refractory TN due to its minimally invasive nature, efficacy, safety, and ability to be performed on an outpatient basis.[20] As the adoption of this technology grows, a study of the existing literature regarding this subject becomes necessary. This bibliometric analysis of the trends in publication and scope of the most-cited articles in the last five decades aims to provide a landscape of the field and identify areas of further research needs.

The publication of highly-cited articles in the field of TN SRS began in 1971. After this initial report, there was a 20-

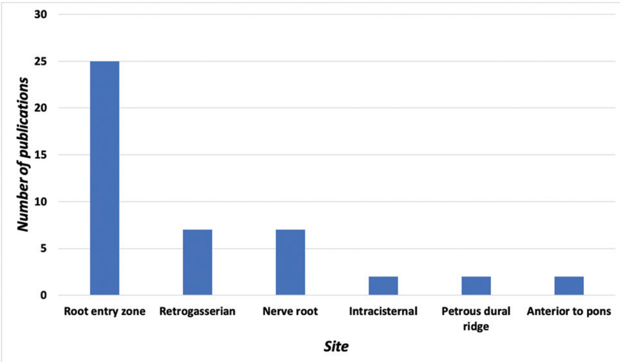

Fig. 7 Categorical distribution of 100 most cited articles per targeted anatomical site.

year gap before another impactful article was published in 1991,[25] reflecting a substantial gap between SRS as a proof-of-concept for TN and its acceptance as a part of the standard armamentarium against TN. Since then, the majority of articles have been case series evaluating the outcomes following Gamma Knife radiosurgery, with ablation of the nerve at the root entry zone being the most commonly-targeted anatomic site. The article with the highest overall citation count was "Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute," authored by Rogers et al in 2000 and published in the *International Journal of Radiation Oncology Biology Physics* with 343 citations and 15.6 citations-per-year.[26] The study assessed the effectiveness and complications of 89 patients who underwent Gamma Knife radiosurgery at their institution from 1997 to 2000. The authors found that 96.3% of patients experienced pain relief, which they had not experienced despite being on maximum doses of standardized pharmacologic therapies. In addition, they found that postoperative facial numbness was predictive of pain relief following the procedure. The second most-cited article was "Stereotactic radiosurgery for trigeminal neuralgia: A multi-institutional study" published by Kondziolka et al in the *Journal of Neurosurgery* in 1996 led to 310 citations and 11.9 citations-per-year.[27] The authors evaluated 50 patients at five different centers who underwent Gamma Knife radiosurgery for TN and concluded that the root entry zone was an appropriate target for SRS and that SRS was an effective modality for the management of medically- and surgically-refractory TN.

Of the articles included in this study, the vast majority (91%) of studies were case series rather than comparative studies. There was one article[28] that described a prospective analysis of a single physician at a single institution's practices on 24 patients. In addition, there was one prospective, double-blind randomized trial published by Lunsford and Flickinger et al using a one versus two isocenter approach which found an increased chance of post-SRS trigeminal sensory loss, but no increased response rate.[29] To further analyze the effectiveness of SRS in TN, it may be warranted to conduct further retrospective and prospective multicentric comparative studies among SRS modalities as well as between SRS and other existing treatment modalities of TN. Moreover, this highlights the need for more generalizable, multi-institution comparative studies to better inform treatment decisions between these modalities and identify the inherent advantages and limitations of each technique.

Gamma Knife Radiosurgery

Eighty-nine percent of the top-cited articles discussed the use of Gamma Knife radiosurgery to alleviate the symptoms of TN. The two most highly-cited articles specifically investigating this modality were "Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute," by Rogers et al and "Stereotactic radiosurgery for trigeminal neuralgia: A multi-institutional study using the gamma unit" by Kondziolka et al.[22,27] Both papers were also the most frequently cited overall. Rogers et al[22] reported that Gamma Knife radiosurgery had similar outcomes of pain relief in comparison to microvascular decompression and radiofrequency rhizotomy (96 vs. 98%, respectively) with none of their patients experiencing anesthesia dolorosa, corneal anesthesia, perioperative morbidity, or mortality. Other studies have also corroborated this article's claim that Gamma Knife radiosurgery has comparable outcomes with fewer postoperative complications.[30] Among all SRS modalities, Gamma Knife radiosurgery still appears to be the most commonly used and well-studied for this application. Only four articles discussed LINAC broadly, while another five discussed CyberKnife specifically. The most highly-cited publication that described the use of LINAC was "Linear accelerator radiosurgery using 90 gray for essential trigeminal neuralgia: Results and dose-volume histogram analysis" by Goss et al in *Neurosurgery* in 2003.[31] The most highly-cited article (one of five) that discussed CyberKnife, in particular, was "CyberKnife radiosurgery for TN" by Romanelli et al in *Stereotactic Functional Neurosurgery* in 2003.[32] Gamma Knife radiosurgery technology was designed specifically for cranial pathology as it allows for radiological accuracy down to 0.15 mm and therefore allows for precise correlation with magnetic resonance and computed tomography images in two-dimensional and three-dimensional views, allowing for improved sparing of surrounding tissue compared with other SRS modalities. Gamma Knife SRS is also typically conducted in one session, another advantage over LINAC and CyberKnife.[33]

Root Entry Zone

The trigeminal root entry zone, with 25 articles, accounted for the most-specified anatomic target site for TN. Of the papers that specified, the three most cited were the Rogers and Kondziolka papers already mentioned and "Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: Implications of treatment and critical review of the literature - Clinical article" by Dhople et al in the *Journal of Neurosurgery* in 2009.[22,27,34] The root entry zone (Obsteiner-Redlich zone) is the point along the proximal trigeminal nerve at which peripheral myelination transitions to central myelination.[24] Anatomically, this area lies approximately 2 cm posterior to the Gasserian ganglion which is often the target of percutaneous treatments.[22] While initial reports demonstrated pain relief with the targeting of the Gasserian ganglion with radiosurgery, further studies showed inconsistent outcomes with that target.[19,25,35,36] Barbaro et al found that there was a direct correlation between the dosage received to the root entry zone and pain relief experienced by the patients.[37] From Barbaro et al's report, and using prior experience with this anatomical region from microsurgery, the root entry zone became the primary target of action.[22] Kondziolka et al identified that the root entry zone could be well-identified on magnetic resonance imaging, lending further credence to its use as a reliable target for SRS.[27]

Multiple Sclerosis Related Trigeminal Neuralgia

While approximately 95% of TN is compressive in etiology, a small but significant etiology of TN is multiple sclerosis leading to demyelination of the nerve.[11] It is known that multiple sclerosis-related TN is often much less responsive to existing medical or surgical interventions and that it has a higher rate of pain recurrence.[38,39] Among the top 100 listed in the present study, seven articles specifically discussed SRS treatment of multiple sclerosis-related TN. Of these, the publication with the highest number of citations was "Gamma knife radiosurgery for trigeminal neuralgia associated with multiple sclerosis" by Rogers et al and published in the *Journal of Neurosurgery* in 2002; this paper had 82 citations.[40] Rogers et al examined 15 patients who underwent Gamma Knife radiosurgery; at a mean follow-up time of 17 months, 80% of patients experienced pain relief. Five patients underwent a second procedure and all experienced improvement. The only noted complication was facial hypesthesia, which was found to also be predictive of positive outcomes. Thus, this paper found that Gamma Knife radiosurgery is an effective treatment for multiple sclerosis-related TN. Another study compared the efficacy of Gamma Knife radiosurgery and percutaneous retrogasserian glycerol rhizotomy in multiple sclerosis-related TN.[41] In that paper, Mathieu et al[41] found that while both strategies were effective, Gamma Knife radiosurgery had a lower complication rate and a latency interval of an average of 6 months before pain relief occurred. Therefore, the authors suggested that multiple sclerosis patients experiencing severe, debilitating TN pain should undergo percutaneous glycerol rhizotomy, regardless of the status of medical management. Given the relative paucity of literature on SRS for TN in multiple sclerosis patients revealed by this bibliometric analysis, this should be considered an area in need of additional investigation.

Limitations

This bibliometric analysis is limited by the methods of the database search. As only the SCOPUS database was used, some articles which were not indexed may have been left out. However, multiple common search terms were employed to increase the likelihood that all relevant papers were included in this study. Because some databases report the number of citations per paper differently (i.e., including non-peer-reviewed works), SCOPUS was used for all citation counts for consistency; however, minor variations in citation counts commonly occur among scientific databases based on indexing criteria. Lastly, papers published earlier accumulate more citations over time, creating a time bias in which newer papers naturally have fewer citations despite the potentially high impact. To correct for this bias, this study utilized the citation-per-year variable as an important indicator of the paper's relative impact rather than its absolute citation count.

Conclusion

There are many highly cited papers on SRS for TN; most are American papers published in neurosurgical journals between 1995 and 2015 focusing on Gamma Knife SRS. SRS has become a preferred modality for the management of TN. While many studies have proven the safety and efficacy of this treatment option, this bibliometric analysis highlights the need for multi-institutional studies comparing different treatment modalities to delineate the role of SRS in TN as well as to provide clarity on its role, safety, and efficacy in noncompressive etiologies, such as multiple sclerosis. Nevertheless, the increase in pain relief with the lower rate of complications of SRS has been reflected by an increasing number of publications that are highly cited in this field in recent years. This study constitutes the first bibliometric analysis in this area and sheds light on the academic contributions and trends in the SRS treatment of TN.

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Conflict of Interest
None declared.

Availability of Data and Material
All data generated or analyzed during this study are included in this article or its online suppl. material files. Further enquiries can be directed to the corresponding author.

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