BMC Neurology

SYSTEMATIC REVIEW

Open Access

Stereotactic radiosurgery for tumor-related trigeminal neuralgia: a systematic review and meta-analysis

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Abstract

Background Tumor-related trigeminal neuralgia (TRTN) accounts for approximately 6% of all facial pain syndromes. Conventional medical treatments have short-term pain relief effects in TRTN cases; however, they are correlated with substantial failure rates of 63–100%. Microsurgical resection (MS) and stereotactic radiosurgery (SRS) are the two primary therapeutic options for the management of TRTNs. This systematic review and meta-analysis evaluated the pain-related outcomes and complications of SRS in TRTNs.

Methods A systematic literature search was conducted on February 24, 2025, comparing PubMed, Embase, Scopus, and Web of Science. Studies reporting pain-related outcomes and adverse radiation effects (ARE) for SRS in TRTNs were included.

Results Nineteen studies with 454 patients were included. Meningioma (67.7%, 304/449) was the most common tumor, followed by vestibular schwannoma (VS) (18.3%, 82/449) and trigeminal schwannoma (8.2%, 37/449). Our meta-analysis demonstrated that SRS is associated with a pooled complete pain-free rate of 38% (95% CI: 27-50%), an adequate pain relief rate of 73% (95% CI: 63-83%), and an ARE rate of 14% (95% CI: 7-22%). In those where the underlying etiology was pertoclival meningiomas, SRS resulted in a pooled complete pain-free rate of 30% (95%CI: 5-64%), an adequate complete pain relief rate of 64% (95%CI: 33-90%), and an ARE rate of 13% (95%CI: 0-48%).

Conclusion SRS is associated with favorable pain-related outcomes and low ARE rates in patients with TRTN. Both tumor-only related and dual-targeted approaches are associated with comparable outcomes.

Keywords Radiosurgery, Gamma knife radiosurgery, Trigeminal neuralgia, Meta-analysis

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Introduction

Trigeminal neuralgia (TN) is a painful chronic neurological disorder characterized by paroxysmal episodes of facial pain along the fifth cranial nerve branches [1–3]. The prevalence of TN is reported to be 0.16–0.3% [4]. TN is classified into three groups: classical, secondary, and idiopathic [1]. Secondary TN is caused by nerve compression caused by multiple sclerosis or space-occupying lesions, including tumors and arteriovenous malformation [5]. Tumor-related TN (TRTN) accounts for approximately 6% of all facial pain syndromes [2]. Benign or malignant tumors located at the cavernous sinus, Meckel's cave, cerebellopontine angle, petrous apex, and petroclival can result in the development of TRTN [2]. Meningiomas and schwannomas are the most frequent cause of TRTNs [2].

The management of TRTN cases is challenging. Conventional medical treatments have short-term pain relief effects in TRTN cases; however, they are correlated with substantial failure rates of 63–100% [6]. Microsurgical resection (MS) is the most effective option for pain relief; however, due to the complex anatomical location, gross total resection may not be achieved, and resection is correlated with morbidity and mortality [2]. On the other hand, MS may not be the optimal therapeutic option for some patients, including the elderly and those with considerable morbidity [2].

Over the past decades, stereotactic radiosurgery (SRS) has been increasingly used to treat various intracranial pathologies, including TNs [7–10]. Several studies have evaluated the efficacy and safety of SRS in managing TRTNs, especially those with meningioma and vestibular schwannoma (VS) [7–25]. A systematic review and meta-analysis published in 2020 by Peciu-Florianu et al., which comprised 13 studies, demonstrated that SRS is associated with a complete pain relief rate of 50.5% and an adequate pain relief rate of 83.8% [2]. Several studies with larger sample sizes have been conducted in recent years, necessitating the incorporation of recent literature into previous meta-analyses. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of SRS in patients with TRTN.

Materials and methods

Objective

This systematic review and meta-analysis, conducted in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guidelines, evaluated the role of SRS in TRTNs [26].

Search strategy

On February 24, 2025, a systematic search was conducted in PubMed, Embase, Scopus, and Web of Science using individualized search queries containing the following keywords and their equivalents: "trigeminal neuralgia," "Radiosurgery," "Meningioma," "Vestibular schwannoma," "trigeminal schwannoma," and "Tumor-related" (Supplementary Table S1). No further filters were used during the search.

Eligibility criteria

The inclusion criteria were as follows:

1. Studies that have evaluated the outcomes and adverse events of SRS in TRTNs.
2. Publications that reported complete pain-free, adequate pain relief, and adverse radiation effect (ARE).
3. Clinical trials, cohort studies, retrospective studies, or case reports with five or more patients.

The exclusion criteria were:

1. Case series with less than five individuals, case reports, book chapters, conference abstracts, preprints, commentaries, and editorials.
2. Lack of reporting of the complete pain-free, adequate pain relief, and ARE.
3. Overlap between the participants of the included studies.
4. Studies published in a language other than English.

Study selection process

The search results were imported into the Covidence Software, and the duplicates were identified and excluded. Two independent reviewers (B.H. and S.T.) conducted the title/abstract and full-text screening, and a third author (I.M.) resolved conflicts. The screening steps were conducted from February 24, 2025, to March 2, 2025. Studies that met the inclusion criteria were enrolled for data extraction.

Data extraction and risk of Bias assessment

Two independent reviewers (P.T. and R.A.) conducted the data extraction process, and a third reviewer (H.S.) resolved any conflicts. The data extraction was conducted for baseline characteristics and SRS-related outcomes. The baseline characteristics section regarding demographic data, such as age, tumor type, gender, and TN distribution. The SRS-related outcomes were follow-up duration, pain-related variables, and ARE. The pain was defined according to the Barrow Neurological Institute (BNI) criteria. Complete pain relief was defined as a BNI score of I. Adequate pain relief was defined as a BNI score of I to III. In cases where a BNI score was not reported, the equivalent criteria used by the authors were considered. The risk of bias (RoB) was evaluated using

the Risk of Bias in Non-randomized Studies—of Interventions tool (ROBINS-1) [27].

Statistical analysis

The R language (R Foundation for Statistical Computing, version 4.4.2) was used for the meta-analysis. The random-effects model was used when I2 exceeded 40% or Cochran's Q was substantial ($P<0.1$). The leave-one-out sensitivity and publication bias were also evaluated for each meta-analysis. Meta-regression was performed to identify potential sources of heterogeneity. A p-value <0.05 was considered statistically significant. The medians were converted to means by the Luo et al. method [28].

Results

Study selection process

The search resulted in the identification of 1,134 studies, of which 500 were duplicates and were excluded (Fig. 1). Of the 634 studies enrolled for title and abstract screening, 568 were deemed irrelevant and were excluded. Sixty-six studies were enrolled for full-text screening, and as a result, 47 were excluded. Across the excluded papers, four were due to overlapping populations [24, 29–31], and four were due to inseparable data from trigeminal neuropathy [32–35]. Ultimately, 19 studies were included in the study.

Risk of bias assessment

The RoB of the included studies demonstrated that most were associated with low or moderate RoB, and only one study showed serious RoB (Supplementary Fig. S1). In the confounding and selection of participants domains, the majority of the included studies demonstrated low to moderate RoB, which results from the retrospective nature of the included studies. The classification of the interventions showed moderate to low RoB in most of the included studies, which demonstrates that in most studies the SRS were defined well. Most of the studies showed low to moderate RoB in deviations from intention, indicating that SRS was delivered as intended. The results of the missing data, outcomes measurement, and result selection domains demonstrated that the outcomes of the included studies were reliable.

Baseline characteristics

Nineteen retrospective studies with 454 patients were included (Table 1). The mean age ranged from 45.2 to 65.3 years. Regarding histology, meningioma (67.7%, 304/449) was the most common tumor, followed by VS (18.3%, 82/449) and trigeminal schwannoma (8.2%, 37/449). Females comprised 75.1% (302/402) of the participants included in this study. Regarding the pain distribution, V2 (22.9%, 43/188) was the most frequent, followed by V2-V3 (21.3%, 40/188) and V1-V2 (19.1%, 36/188). The SRS modality consisted of gamma knife radiosurgery, except for one that utilized Cyberknife radiosurgery. The mean tumor volume ranged from 1.97 to 12.5, respectively.

Stereotactic radiosurgery outcomes

Table 2 demonstrates the outcomes following SRS. The mean follow-up ranged from 19 to 149 months. The complete pain-free rate and adequate pain relief rates ranged from 5.7 to 78.4% and 28–100%, respectively. The ARE rates ranged from 0 to 43% across the included studies.

Meta-analysis of outcomes

The meta-analysis demonstrated that SRS is associated with a pooled complete pain-free rate of 38% (95% CI: 27-50%), showing high heterogeneity (I^2=81.6%, $P<0.001$) (Fig. 2A). The meta-analysis revealed a pooled adequate pain relief rate of 73% (95% CI: 63-83%), also with high heterogeneity (I^2=74.8%, $P<0.001$) (Fig. 2B). The meta-analysis for the ARE exhibited a pooled ARE rate of 14% (95% CI: 7-22%), characterized by high heterogeneity (I^2=66.6%, $P=0.0001$) (Fig. 3C).

Five studies were included in the meta-analysis of complete pain-free status in patients with petroclival meningioma (Fig. 3A). The meta-analysis revealed a pooled complete pain-free rate of 30% (95% CI: 5-64%) with high heterogeneity (I^2 = 75.8%, $P=0.002$) (Fig. 3A). For adequate complete pain relief, the meta-analysis reported a rate of 64% (95% CI: 33-90%) with high heterogeneity (I^2 = 76.8%, $P=0.0006$) (Fig. 3B). The meta-analysis for the ARE in patients with petroclival meningioma revealed a pooled ARE rate of 13% (95% CI: 0-48%) with high heterogeneity (I^2 = 64.6%, $P=0.037$) (Fig. 3C). A GRADE assessment demonstrated that the overall certainty of the evidence was moderate for all three outcomes (Supplementary Table S3).

Sensitivity analysis

The leave-one-out sensitivity analysis for the complete pain-free rate demonstrated that, despite high heterogeneity, the results remain stable and that the omission of each study did not significantly impact the results (Supplementary Fig. S2A). Similarly, the sensitivity analysis for the adequate pain relief rate revealed consistent results (Supplementary Fig. S2B). The sensitivity analysis for the ARE showed that the omission of each study did not significantly affect the pooled estimate (Supplementary Fig. S2C).

Publication bias

The funnel plot for the complete pain-free rate showed some asymmetry; however, Egger's test ($P=0.53$) revealed no significant publication bias (Supplementary Fig. S3A).

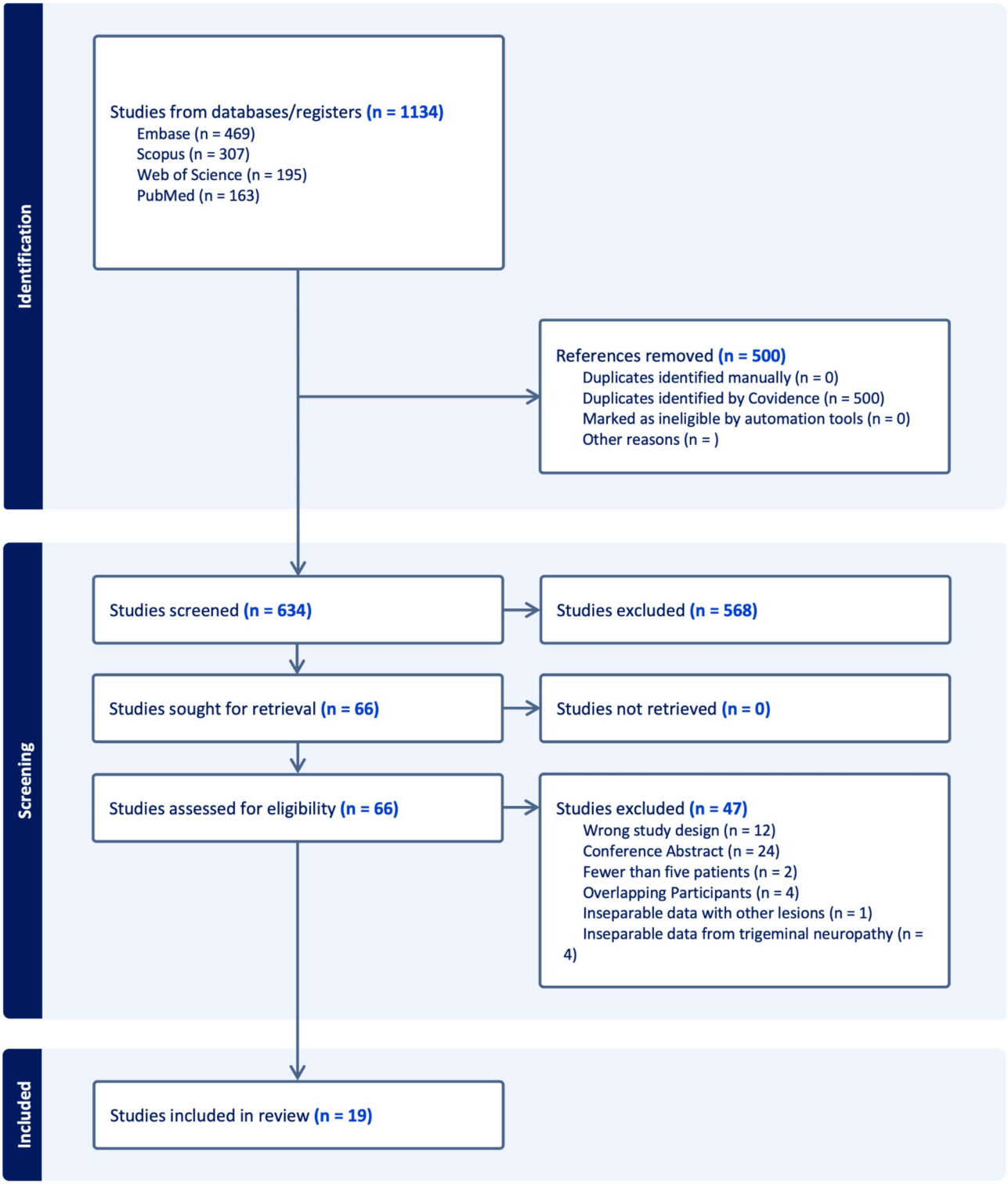

Fig. 1 PRISMA flowchart of the current study

The funnel plots for adequate pain relief and ARE displayed a relatively symmetrical pattern, and Egger's test ($P = 0.66$ and $P = 0.74$) indicated no significant publication bias (Supplementary Fig. S3C-D).

Discussion

The current systematic review and meta-analysis showed that SRS is a proper therapeutic option for managing individuals with TRTN. Our meta-analysis demonstrated

Table 1 Baseline characteristics of patients, lesions, and SRS

Study	Country	Recruitment Period	Patients	Mean age	Gender (M/F)	Histology				Pain distribution						Pain distribution				SRS			
						Men	VS	TS	Other	V1	V2	V3	V1-V2	V2-V3	V1-V2-V3	Resection	SRS	Resectino + SRS	Other interventions	SRS modality	Mean prescribed dose (Gy)	Tumor volume (cm3)	Target type
Nguyen 2025	Vietnam	2016–2022	44	45.7	9/35	30	5	9	0	3	10	2	11	11	7	3	6	2	2	GKRS	NA	4.9	Tumor&TN
Sahoo 2024	India	2012–2023	50	50	19/31	27	19	0	4	0	11	12	18	6	3	0	0	0	0	GKRS	13.7	7.16	Tumor
Franzini 2023	Italy	2014–2020	6	63.8	NA/NA	5	1	0	0	1	3	0	0	1	1	0	5	0	0	GKRS	NA	NA	TN
Hall 2022	USA	2009–2021	21	62.3	10/11	9	4	0	8	NA	NA	NA	NA	NA	NA	3	0	0	0	CKRS	NA	3.734	Tumor&TN
Chung 2022	South Korea	1994–2016	14	NA	NA/NA	0	0	14	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GKRS	NA	NA	NA
Hegazy 2022	Egypt	2010–2020	25	52.1	5/20	25	0	0	0	NA	NA	NA	NA	NA	NA	0	0	0	0	GKRS	13	12.5	Tumor
Park 2020	South Korea	2009–2019	35	58.5	4/31	35	0	0	0	1	8	5	2	3	15	0	0	0	0	GKRS	13.2	5.3	TN
Sadik 2018	Netherlands	2003–2015	23	NA	NA/NA	23	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GKRS	NA	NA	Tumor
Chivukula 2017	USA	1997–2014	12	59.8	4/8	8	1	0	3	0	2	4	1	5	1	2	3	0	7	GKRS	NA	NA	TN
Park 2016	South Korea	2006–2015	21	56.5	0/21	20	1	0	0	2	1	4	3	7	4	1	0	0	1	GKRS	12.5	3.3	TN
Kim 2016	South Korea	1998–2013	15	65.3	6/9	11	3	1	0	NA	NA	NA	NA	NA	2	0	0	0	0	GKRS	NA	1.97	Tumor&TN
Cho 2016	South Korea	2002–2011	50	55.05	11/39	30	11	7	2	NA	NA	NA	NA	NA	NA	8	1	0	2	GKRS	NA	NA	Tumor
Bir 2016	USA	1995–2014	6	45.2	3/3	6	0	0	0	0	4	0	0	2	0	4	2	0	0	GKRS	NA	NA	Tumor&TN
Squire 2012	USA	1999–2010	21	65.1	4/17	14	5	2	0	NA	NA	NA	NA	NA	NA	0	0	0	0	GKRS	NA	3.8	Tumor
Kano 2011	USA	NA	12	55.8	2/10	12	0	0	0	0	4	2	1	5	0	0	0	0	1	GKRS	NA	6.8	Tumor
Huang 2008	Taiwan	1999–2004	10	53.7	3/7	6	4	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	GKRS	NA	7.16	Tumor&TN
Régis 2001	France	1992–1997	53	53.5	14/39	24	17	1	6	NA	NA	NA	NA	NA	NA	25	0	0	0	GKRS	NA	NA	Tumor&TN
Chang 1999	South Korea	1991–1998	27	51.8	6/21	14	10	1	2	NA	NA	NA	NA	NA	NA	14	0	0	0	GKRS	NA	7.5	Tumor
Young 1997	USA	NA	9	NA	NA/NA	5	1	2	1	NA	NA	NA	NA	NA	NA	2	0	0	1	GKRS	NA	6.06	Tumor

NA: Not available, M: Male, F: Female, MEN: meningioma, VS: Vestibular schwannoma, TS: Trigeminal schwannoma, SRS: Stereotactic Radiosurgery, GKRS: Gamma knife radiosurgery, CKRS: Cyberknife radiosurgery

Table 2 Clinical and radiological outcomes

Study	Pain-free (%)	Adequate pain relief (%)	ARE (%)
Nguyen 2025	43.2%	86.4%	31.8%
Sahoo 2024	16%	64%	14%
Franzini 2023	33.3%	33.3%	33.3%
Hall 2022	41.7%	58.3%	42.9%
Chung 2022	21.4%	64.3%	NA%
Hegazy 2022	NA	28%	NA%
Park 2020	5.7%	74.3%	25.7%
Sadik 2018	30.4%	56.5%	8.7%
Chivukula 2017	50%	83.3%	25%
Park 2016	23.8%	71.4%	0%
Kim 2016	46.7%	86.7%	19%
Cho 2016	40%	95%	NA%
Bir 2016	66.7%	100%	NA%
Squire 2012	33.3%	81%	9.5%
Kano 2011	41.7%	75%	0%
Huang 2008	70%	70%	20%
Régis 2001	78.4%	92.2%	3.8%
Chang 1999	18.5%	44.4%	7.4%
Young 1997	77.8%	88.9%	11.1%

NA: Not available, FU: Follow-up, ARE: Adverse Radiation Effect, Pain-free was defined as Barrow Neurological Institute (BNI) score of I, and Adequate pain relief was defined as BNI I-III

that SRS is associated with a pooled complete pain-free rate of 38% (95% CI: 27-50%), an adequate pain relief rate of 73% (95% CI: 63-83%), and an ARE rate of 14% (95% CI: 7-22%). In addition, our findings suggested that for those whose TN was caused by compression by petroclival meningioma, SRS resulted in a pooled complete pain-free rate of 30% (95%CI: 5-64%), adequate complete pain relief rate of 64% (95%CI: 33-90%), and ARE rate of 13% (95%CI: 0-48%). Our findings underscored that SRS is correlated with promising pain-related outcomes and low ARE rates.

Peciu-Florianua et al. conducted a meta-analysis that reviewed the literature until December 2019 and included 13 studies [2]. They demonstrated that SRS was associated with a complete pain relief rate of 36.4%, based on five studies, and an adequate pain relief rate of 41.2%, based on three studies [2]. The adequate pain relief rate was higher in our study, probably due to the higher number of included studies. They also showed that complications occurred at a pooled rate of 12.6% [2]. Another systematic review by Nugroho et al., which reviewed the literature until December 2021, showed that SRS was associated with pain improvement in 79.1% of cases [3].

MS and SRS are the two main therapeutic options for managing TRTNs [2]. MS mitigates tumor volume and subsequent mass effect on the trigeminal nerve [2]. A recent systematic review by Nugroho et al. showed that MS was associated with improved pain status in 92.2% of the cases [3]. Prior studies suggested that nerve root decompression was associated with adequate

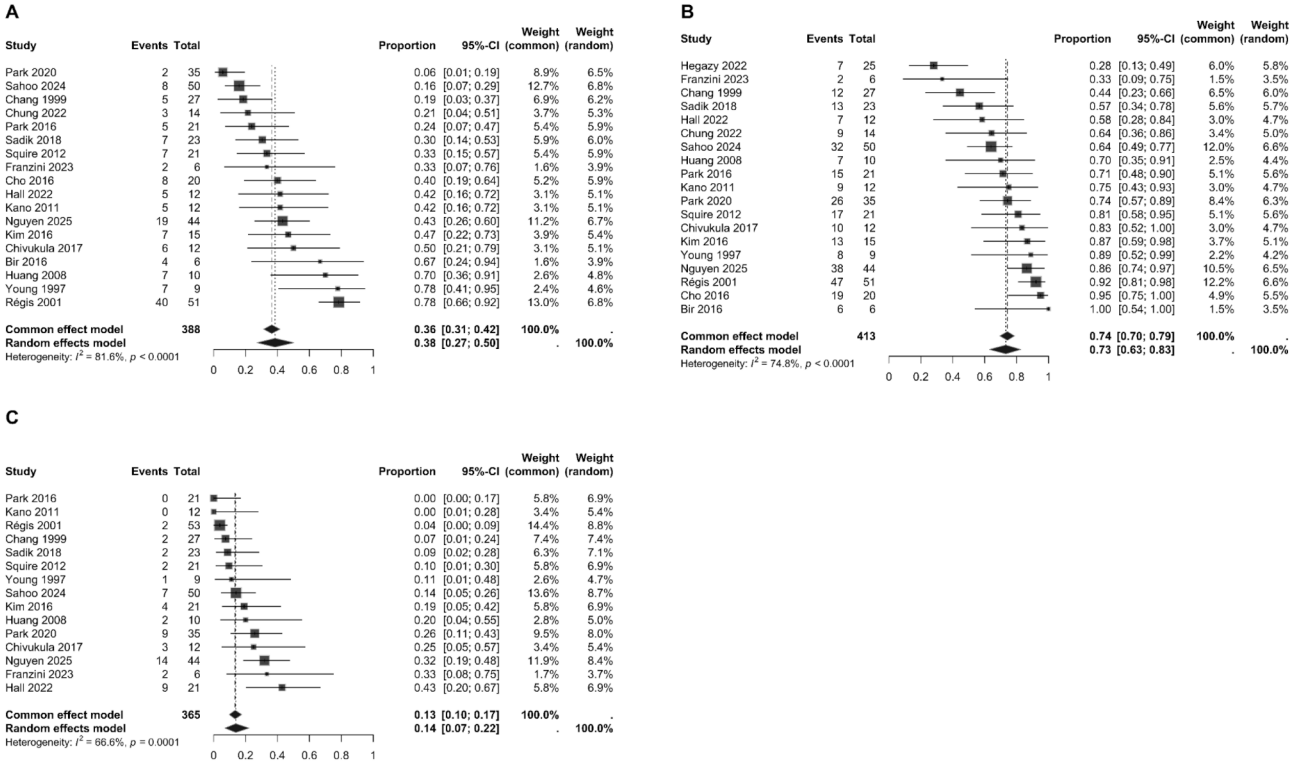

Fig. 2 Proportion meta-analysis of (**A**) complete pain-free rate, (**B**) adequate pain relief rate, (**C**) ARE rate

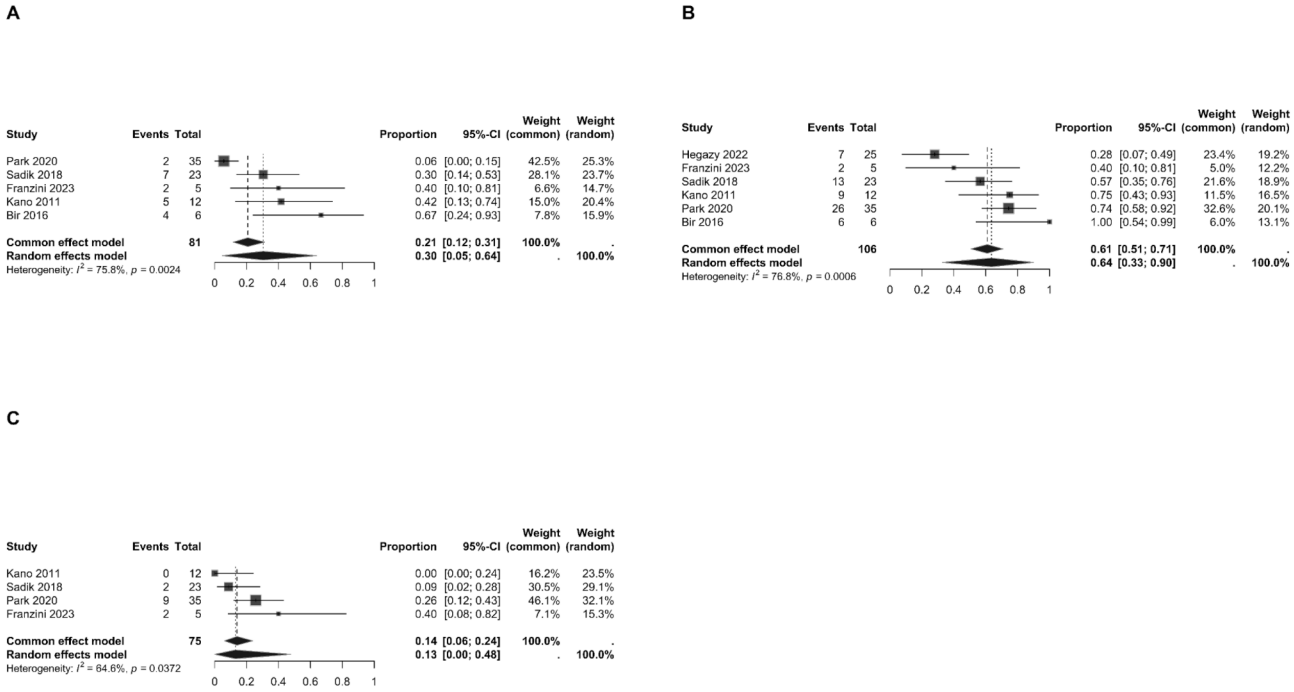

Fig. 3 Proportion meta-analysis of (**A**) complete pain-free rate, (**B**) adequate pain relief rate, (**C**) ARE rate in those with petroclival meningioma

compression-related pain manifestations in tumor or vascular-related TNs [3, 36]. Although previous studies demonstrated that subtotal resection that results in nerve root decompression is associated with alleviation of the pain symptoms, it is accompanied by high rates of pain recurrence [3]. Nugroho et al. demonstrated in their systematic review that MS with gross total resection was superior to SRS in managing TR-TN patients, as none of the cases in the MS group experienced symptom worsening, whereas 6.6% of the SRS group experienced worsening of symptoms [3]. They suggested that MS with gross total resection is the main option in patients with MS-TN, and SRS can be considered in patients who are not proper surgical candidates [3].

On the other hand, previous studies and our findings demonstrated that SRS is associated with substantial rates of adequate pain relief and low adverse effects [3]. The underlying mechanism of SRS in TRTN remains unknown [7]. The pain in the TRTN results from nerve compression by the lesion itself or the displaced vessels [7]. The primary effect of SRS on pain symptoms is attributed to the reduction in lesion size and subsequent nerve decompression [7]. Nevertheless, previous studies demonstrated that in most cases, pain relief occurs earlier than the shrinkage of the lesion and stated that there is no direct association between pain relief and volume reduction [3, 7, 21, 24, 34]. Therefore, alleviating the pain is directly attributed to the radiation effect, which leads to nerve demyelination, resulting in pain relief [2, 7, 23, 37].

In the setting of the TRTNs, both the lesion and the trigeminal nerve can be irradiated by SRS [7]. Nguyen et al. targeted both the lesion and the trigeminal nerve, demonstrating that a dual-targeted approach yielded a significant pain relief rate of 86.4% with a median latency period of two months [7]. Kim et al. also conducted dual-targeted SRS, demonstrating that 86.7% of patients experienced pain relief over a 38-month follow-up period [17]. Sahoo et al. conducted SRS targeting only tumors and showed that adequate pain relief was achieved in 77.7% of those with both tumor size decree and nerve was completely free from the lesion, 65.2% of those with tumor size decree but tumor adherent to the nerve, and 55.5% in those that nerve was not separated [8]. Kano et al. demonstrated that in a cohort where only tumors were irradiated, 83% of the cases achieved adequate pain relief [21]. The following studies should directly compare dual-targeted or tumor-targeted approaches to determine which approach is superior.

A frequent subset of lesions that cause TRTN are petroclival meningiomas. Like the other causes, MS or SRS can manage petroclival meningioma-related TNs [38, 39]. Park et al. compared MS and SRS in a cohort of 70 patients with newly diagnosed petroclival meningioma [13]. They demonstrated that pain relief was achieved in 37% of SRS and 91% of MS patients [13]. A recent meta-analysis by Byun et al. demonstrated that MS (89%) was associated with significantly higher rates of TN improvement than SRS (37%) ($P < 0.01$) [39]. In addition, they showed that pain-free rates without medication were

significantly higher in the MS (90.7%) than in the SRS (34.5%) ($P<0.01$) [39]. Similarly, another systematic review by Hallak et al. showed that MS (82%) was associated with a higher rate of pain resolution than SRS (31%) ($P=0.004$) [38]. Additionally, MS was associated with lower rates of pain persistence (0% vs. 25%, $P=0.001$) and pain exacerbation (0% vs. 12%, $P=0.001$) [38]. Our findings also showed that SRS was associated with a 30% pain-free rate and an adequate pain-relief rate of 64%. As previous studies have demonstrated, MS is superior to the SRS in managing TN due to petroclival meningiomas and is the first-line therapeutic option. SRS is an alternative option for those who are not proper candidates for MS.

The application of SRS as a tumor-only, nerve-only, or dual-targeted approach is an important factor in the management of TR-TN patients. The decision should be based on the radiological characteristics and anatomical location of the lesion, including the lesion's volume and its proximity to the trigeminal nerve. In cases where mass effect and nerve compression are both present, dual-targeted SRS may be preferred. When only one of these factors is present, it can assist physikons in choosing between tumor-only or nerve-only approaches. Future studies should focus on evaluating these approaches to optimize the treatment protocol for TR-TN patients.

The decision-making regarding the selection of the optimal therapeutic option in managing TR-TNs should be based on patient-related and tumor-specific factors. In cases where gross total resection is achievable, MS is generally considered the preferred therapeutic option, especially in patients with apparent nerve compression caused by the lesion. SRS can be the preferred option for patients who do not wish to undergo surgery, those in high-risk locations, with deep-seated lesions, or with inaccessible tumors. Underlying histopathology is another important factor, as malignant lesions should preferably be treated with MS rather than SRS. In contrast, lesions such as VS or meningioma can be treated based on their size and location.

Our studies have several limitations. Most were retrospective, which may introduce selection bias and limit the generalizability of the current study's findings. The meta-analyses in our studies revealed high heterogeneity, which may be attributed to variations in tumor histology, tumor or nerve-targeted approaches, lesion size, and follow-up periods. Another limitation is that although most of the included studies reported BNI scores, a few studies did not report BNI scores and used other criteria. Another limitation of our study was that we were unable to conduct a subgroup analysis based on histology, lesion volume, and prior therapeutic interventions. Further studies should focus on evaluating these influential factors to optimize therapeutic options. Variations in the follow-up duration across the included studies were another limitation of our study. Reasonably, longer follow-up durations can be associated with higher rates of pain recurrence and inferior pain-related outcomes.

Conclusion

MS and SRS are the main therapeutic options for patients with TRTN who do not respond to medical treatment. SRS is associated with favorable pain-related outcomes and low ARE rates in patients with TRTN. Both tumor-only related and dual-targeted approaches are associated with comparable outcomes. Although SRS is associated with reasonable results in patients with petroclival meningioma-related TN, MS remained the first-line therapeutic option for these patients.

Abbreviations

TN	Trigeminal neuralgia
TRTN	Tumor-related trigeminal neuralgia
MS	Microsurgical resection
SRS	Stereotactic radiosurgery
VS	Vestibular schwannoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ARE	Adverse radiation effect
BNI	Barrow Neurological Institute
ROBINS-I	Risk of Bias In Non-randomized Studies—of Interventions tool

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04204-6.

Supplementary Material 1

Acknowledgements

None.

Author contributions

Conceptualization: B.H., M.H., Methodology: B.H., M.H., Literature Search: B.H., I.M., S.T., Data Extraction: P.T., M.A., S.H., Risk of Bias Assessment: B.H., E.R., Statistical Analysis: B.H., Writing - Original Draft: B.H., I.M., S.T., A.H., Writing - Review & Editing: B.H., S.T., M.H., R.H., Supervision: B.H., Project Administration: B.H., Revision: D.N. and A.E.

Funding

There is no funding source that the authors declare.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Disclosure

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Ethical approval

The study is deemed exempt from receiving ethical approval.

Consent to participate
Not applicable.

Consent to publish
Not applicable.

Clinical trial number
Not applicable.

Received: 7 April 2025 / Accepted: 23 April 2025
Published online: 03 May 2025

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