Clinical Study

Trigeminal Neuralgia Secondary to Meningiomas and Vestibular Schwannoma Is Improved after Stereotactic Radiosurgery: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Trigeminal neuralgia (TN) secondary to tumors is encountered in up to 6% of patients with facial pain syndromes and is considered to be associated with tumors affecting the trigeminal nerve pathways. The most frequent are meningiomas and vestibular schwannomas (VS). Stereotactic radiosurgery (SRS) has emerged as a valuable treatment, with heterogeneity of clinical results. We sought to review the medical literature on TN treated with SRS for meningiomas and VS and investigate the rates of improvement of TN symptoms. ***Methods:*** We reviewed articles published between January 1990 and December 2019 in PubMed. Pain relief after SRS, the maintenance of pain relief, and TN recurrence and complications were evaluated with separate meta-analyses, taking into account the data on individual patients. ***Results:*** Pain relief after SRS was reported as Barrow Neurological Institute (BNI) pain intensity scores of BNI I in 50.5% (range 36–65.1%) of patients and BNI I–IIIb in 83.8% (range 77.8–89.8%). There was no significant difference in series discussing outcomes for tumor targeting versus tumor and nerve targeting. Recurrences were described in 34.7% (range 21.7–47.6; tumor targeting). Maintenance of BNI I was reported in 36.4% (range 20.1–52.7) and BNI I–IIIb in 41.2% (range 29.8–52.7; tumor targeting series). When both the nerve and the tumor were targeted, only 1 series reported 86.7% with BNI I–IIIb at last follow-up. Complications were encountered in 12.6% (range 6.3–18.8; tumor targeting series) of patients; however, they were much higher, as high as 26.7%, in the only study reporting them after targeting both the nerve and the tumor. The most common complication was facial numbness. ***Conclusion:*** SRS for TNB secondary to

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benign tumors, such as meningiomas and VS, is associated with favorable clinical course, but less favorable than in idiopathic TN. There was, however, heterogeneity among reports and targeting approaches. Although targeting both the nerve and the tumor seemed to achieve better long-term results, the rate of complications was much higher and the number of patients treated was limited. Future clinical studies should focus on the standard reporting of clinical outcomes and randomization of targeting methods.

Introduction

Idiopathic trigeminal neuralgia (TN) is frequently generated by nerve dysfunction due to the vascular compression of the trigeminal nerve root as it enters the brainstem. Microvascular decompression remains the standard treatment modality, whenever feasible [1, 2]. Other alternatives are radiofrequency lesioning, glycerol rhizotomy, balloon percutaneous compression [3], and radiation techniques. It has been acknowledged that stereotactic radiosurgery (SRS) alleviates idiopathic TN with very few side effects [4, 5].

TN secondary to tumors is encountered in up to 6% of patients with facial pain syndromes and is considered to be associated with tumors affecting the trigeminal nerve [6–9]. These tumors are confined to the TN pathways and might include cavernous sinus, Meckel's cave, cerebellopontine angle, petrous apex, petroclival, and can be benign or malignant, e.g., meningiomas, trigeminal schwannomas, vestibular schwannomas (VS), epidermoid cysts, metastasis, and so on [6–8, 10]. Meningiomas and schwannomas are the most common tumors to cause secondary TN. Medication alone has a short-term effect, with a high failure rate, ranging from 63 to 100% [8]. Microsurgical resection is the most effective means of relieving pain, but some tumors cannot be completely excised and resection is associated with morbidity and mortality [6–8]. Also, in patients with an excessive surgical risk, including the elderly, or those with significant comorbidities, open microsurgical resection might not be the treatment of choice. Moreover, if the tumors fill in the trigeminal cistern, transovale needle placement is not feasible. In this context, and during the past 2 decades, SRS has been considered a valuable alternative to microsurgical resection.

Here, we focus on the outcomes of SRS for secondary TN generated by benign tumors, particularly the most common ones, meningiomas and VS [6, 7]. Only a few studies have been dedicated to the treatment of tumor-related facial pain with radiosurgery. In the literature, different targeting strategies and a heterogeneity of clinical results are reported. Hence, there is a need to better understand outcomes and further improve the selection of patients for this indication.

Materials and Methods

Article Selection and Data Extraction

A PubMed search was performed for entries between January 1990 and December 2019 using the following query guidelines: ([trigeminal AND (radiosurgery OR Gamma Knife)] AND [vestibular schwannoma]; or combinations with [meningioma], [skull-base], [benign skull-base]). The beginning of the 1990s was chosen as the starting date because prior to this, there were only a few studies published on meningiomas and VS in general that included SRS. Inclusion criteria required that each article be a peer-reviewed clinical study or a case series of meningiomas and VS treated with SRS, independent of the device (Linear Accelerator-Linac; Gamma Knife, GK) used. As such, case reports, non-English studies, conference papers, and abstracts were not included. Some studies advocated targeting the tumor (most [9, 11–20]), while others advocated targeting the tumor and the nerve (the minority [21, 22]). If a study reported a vast majority of meningiomas and VS and only 1–2 cases of other pathologies, it was included in our analysis. Exclusion criteria were: cases treated with fractionated radiotherapy (unless this was the minority in a larger series) [12], series reporting 2 procedures (only reported by Huang et al. [14]), or series focusing on trigeminal schwannomas which are reputed to have different results and only 1 target (the tumor) [23]. Were also excluded series reporting malignant lesions, as these have a different radiobiology and α-to-β ratio [24]. The article selection is illustrated in Figure 1, which includes studies detailed in Tables 1 and 2. Two separate reviewers applied the inclusion criteria to the PubMed search result; there were no disagreements. Moreover, 4 separate reviewers applied the exclusion criteria to the articles that remained, and we finally included 13 series [9, 11–22].

This study was performed in accordance with the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. In extracting data from these studies, we paid attention to the classical outcomes usually described after SRS for idiopathic TN as per individual patient (in studies individually reporting the outcomes), i.e., pain relief after SRS, pain recurrence, the maintenance of pain relief, and complications [4, 5]. Freedom from pain was evaluated whenever possible using Barrow Neurological Institute (BNI) pain intensity scores of I = no trigeminal pain and no medication; II = occasional pain, but not requiring medication; III = some pain, but adequately controlled with medication; IV = some pain, but not adequately controlled with medication; and V = continuous severe pain or no pain relief [26].

With regard to the radiology aspect, the probability of an incorrect diagnosis based only upon neuroimaging findings in the absence of histology was previously evaluated by Flickinger et al. [27] as 1.4%. All studies analyzed here stated that all cases had typical imaging features of meningiomas and VS. One series, by Kano et al. [15], applied a unique protocol where all patients received an intravenous dose of 20–40 mg of methylprednisolone after radiosurgery.
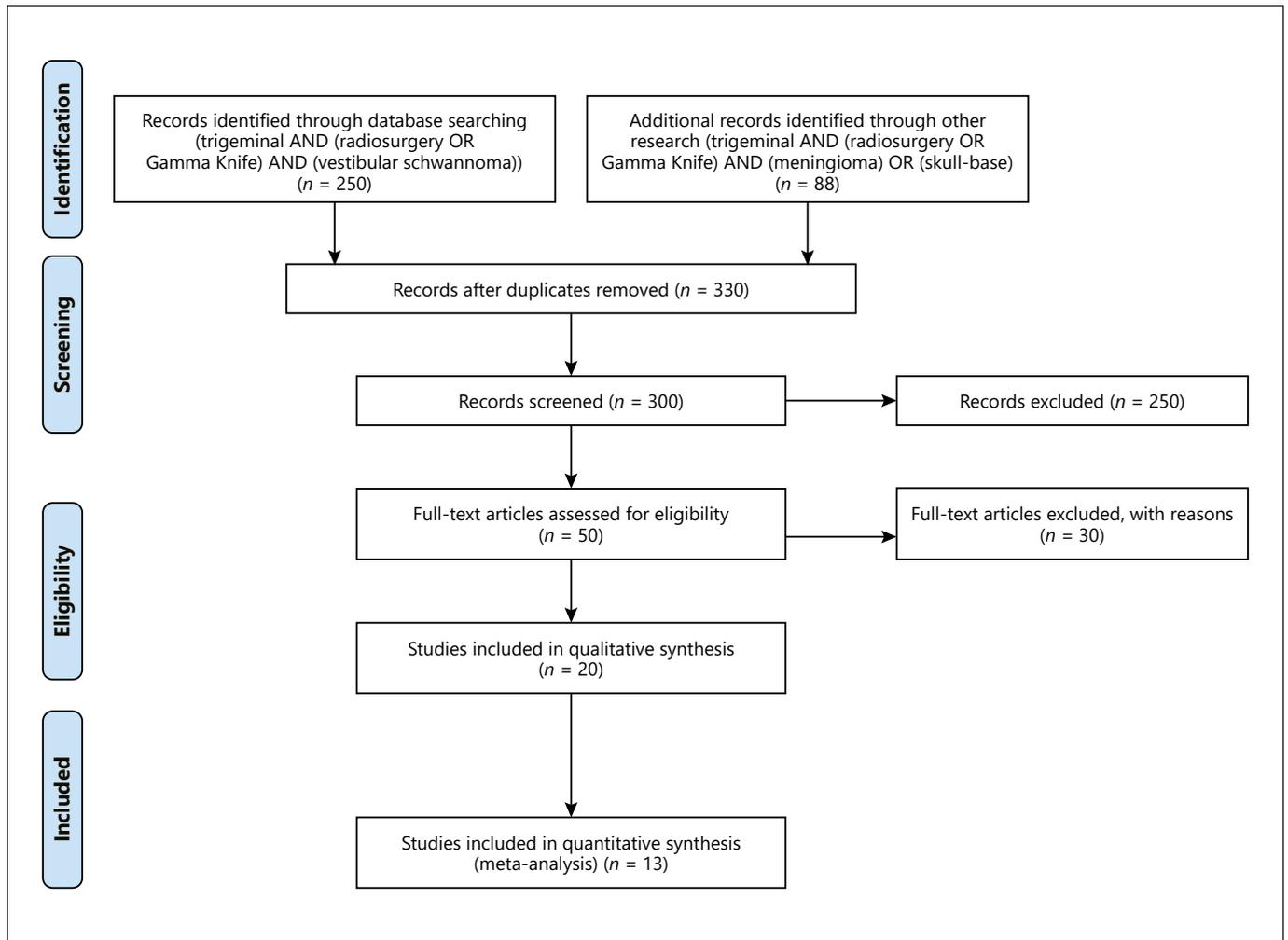
Fig. 1. Flow chart describing study selection according to the PRISMA statement.

Statistical Analysis Using OpenMeta (Analyst) and a Random-Effects Model

Due to the high variation in study characteristics, a statistical analysis using a binary random-effects model (DerSimonian-Laird method) was performed. We used OpenMeta (Analyst) from the Agency for Healthcare Research and Quality.

Weighted summary rates were determined using meta-analytical models. Testing for heterogeneity was performed for each meta-analysis. Pooled estimates using meta-analytical techniques were obtained for all the individual outcomes previously described in the same section.

Results

Pain Relief after SRS

Pain relief after SRS was associated with a higher maximum dose and single-branch involvement [19].

Tumor Targeting Series

Pain relief after SRS BNI I was reported in 52/103 cases, i.e., a rate of 50.5% (range 36–65.1; $I^2 = 58.4\%$, $p_{heterogeneity} = 0.035$, $p < 0.001$; Fig. 2a). Pain relief after SRS BNI I–IIIb was encountered in 189/228 cases, i.e., a rate of 83.8% (range 77.8–89.8; $I^2 = 32.69\%$, $p_{heterogeneity} = 0.147$, $p < 0.001$; Fig. 2b).

Tumor and Nerve Targeting Series (in the Same Session or Separate Sessions)

Pain relief after SRS BNI I–IIIb was encountered in 29/36 cases, i.e., a rate of 83.7% (range 62.3–90.8; $I^2 = 71.1\%$, $p_{heterogeneity} = 0.063$, $p < 0.001$; Fig. 2c). Time to pain relief is reported in Table 2. Time to decrease in tumor volume was considered longer than time to TN response (18.6 vs. 5.3 months) [11].

Table 1. Tumor incidence, follow-up, duration of symptoms prior to SRS, dose, target, target volumes and tumor decrease/control

First author [ref.], year	Tumor incidence and type	Duration of follow-up, months	Duration of symptoms, months (range)	Dose, Gy (range)	Target	Target volume, mL (range)	Tumor decrease, control
Young [20], 1997 (*n* = 9)	–	20 (8–29)		15.7 (10–20)	the tumor	6.1 (1–15.7)	
Chang [11], 1999 (*n* = 27)	14 (51.9%) M 11 (40.7%) VS 1 (3.7%) cancer of the nasopharynx 1 (3.7%) chordoma	32.1	23 (0.7–89)	26.4 (16–35)	the tumor	7.5 (1.3–23.3)	14/25 (56%), –
Pollock [9], 2000 (*n* = 9)	M	45 (12–90)	–	18 (16–20)	the tumor	9.7 (1.9–27.2)	–, 15/16 (93.8%)
Régis [17], 2001 (*n* = 53)	Group IV: 24 (45.3%) M, 17 (32.1%) VS, 2 (3.8%) metastasis, 2 (3.8%) CSM, 2 (3.8%) HPC, 1 (1.9%) PA	55.2 (2–84)	–	II 80–90 III 15.3 (12–20) IV 14.2 (8–25)	II: the nerve (cistern) (*n* = 3) III: the part of the tumor that supposedly included the nerve (*n* = 4) if the nerve root could not be identified IV: the tumor (*n* = 46)	–	–
Kreil [16], 2005 (*n* = 23)	–	–	–	–	–	–	–
Huang [14], 2008 (*n* = 21)	12 (57.1%) M 9 (42.9%) VS	57.8 (36–94)		men: 12.7 (12-15) VS: 13 (11.5–16)	the tumor	men: 8.2 (1.1–21) VS: 5.6 (2–9.2)	17 (80%), 100%
Kano [15], 2011 (*n* = 12)	12 (100%) PCM	68 (25–180)	31 (1.3–120.3)	13 (11–16)	the tumor	3.8 (1–15.9)	
Squire [18], 2012 (*n* = 21)	15 (71.4%) M 4 (19.1%) VS 2 (9.5%) TS	45.6	–	12 (11–13)	the tumor	–	–
Tanaka [19], 2013 (*n* = 31)	17 (54.8%) PFM 9 (29%) CSM 5 (16.1%) TS	50 (12–184)	18.3±23.4 (0.5–84)	15 (13–20)	1 (3%) the tumor and nerve the tumor (*n* = 30)	7.7 (1.5–34.8) (PIV)	19 (61%) decrease, 11 (35%) stable
Chivukula [12], 2017 (*n* = 12)	12 (100%) M	55.6 (10.3–125.3)	–	13 Gy, 14 Gy for tumor 50.4 and 57.6 FRT 90 Gy for nerve targeting	initially the tumor (*n* = 10) followed by the nerve (*n* = 12)	–	–
Cho [13], 2016 (*n* = 50)	30 (60%) M 11 (22%) VS 7 (14%) TS 1 (2%) EC 1 (2%) AVM	54.8 (13–142)	–	13.25 (10–25) for M 12.5 (12–15) for VS 14 (12–15) for TS 32 for AVM 90 Gy for the nerve	42 (84%) the tumor 2 (4%) the trigeminal nerve 6 (12%) lesion targeted with a boost on the trigeminal nerve if it was visible	–	–, 44/50 (95.7%)
Kim [21], 2016 (*n* = 15)	11 (73%) M 3 (20%) VS 1 (7%) TS	38 (12–78)	–	13 (12.5–15) M 12 (11–13) VS 15 TS 80 (70–85) REZ	A single session, both the tumor and the nerve (REZ)	1.7 (0.1–4.9)	–
Park [22], 2016 (*n* = 21)	21 (100%) M	44.4±32.4 (12–108)	–	12.5±1.1 90	Two sessions: 1– the tumor 2– (after 62±52 months) the trigeminal nerve	3.3±2.83	12/15 (80%), 15/15 (100%)

AVM, arteriovenous malformations; CSM, cavernous sinus meningioma; EC, epidermoid cyst; HPC, hemangiopericytoma; M, meningioma; PA, pleomorphic adenoma; PCM, petroclival meningioma; PFM, posterior fossa meningioma; VS, vestibular schwannoma; TS, trigeminal schwannoma; REZ, root entry zone; FRT, fractionated radiotherapy.

Table 2. Clinical outcomes and further surgeries (when applicable)

First author [ref.], year	Patients experiencing an initial improvement	Time to pain relief, months	Patients with pain recurrence	Time to recurrence, months	Patients with a lasting response	Actuarial[a], years	Patients undergoing craniotomy after SRS, repeat SRS	Patients experiencing complications
Young [20], 1997 (n = 9)	7 (77.8%) BNI I	–	1 (11.1%)	–	7 (77.8%) BNI I	–	–	–
Chang [11], 1999 (n = 27)	24 (85.7%)	5.7 (0.5–49) 11.3 until pain-free	12/24 (50%)	10.3 (2.5–34.5)	12 (42.9%) BNI I–IIIb 5 (18.5%) BNI I 7 (25.9%) pain reduced by >50%	0.5: 28.6% 1: 48.7% 2: 48.7%	3 (11.1%) 2 VS (1 with neurovascular conflict), 1 chordoma (hemorrhage)	6 (22.2%) 3 (11.1%) numbness
Pollock [9], 2000	5/9 (55%) BNI I	–	3/12 (25%)	–	9/24 (37.5%)	–	–	–
Régis [17], 2001 (n = 53)	Overall: 41/46 (89.1%) pain-free According to study classification: II 3/4 (75%) III 2/3 (66.6%) IV 35/46 (79.5%) pain-free, 7/46 (15.9%) improved, 2/46 (4.5%) no answer	–	6/46 (13.3%)	21.5	–	–	–	2/46 (4.3%) IV hypoesthesia
Kreil [16], 2005 (n = 23)	16 (69.6%)	–	–	–	–	–	–	2/16 (12.5%)
Huang [14], 2008 (n = 21)	12 (57%) 17 (81%)	10.5 (2–24)	8/17 (47.1%)	–	–	–	–, 8 (38.1%) trigeminal root/ganglion	4 (19%) facial numbness
Kano [15], 2011 (n = 12)	3 (25%) BNI I 10 (83%) BNI I–IIIb	4 (0.25–10)	3/10 (33.3%)	9.7 (6–12)	5 (41.7%) BNI I 6 (50%) BNI I–IIIb	BNI I–IIIb 1: 80% 2: 74% 3: 66% 5: 55%	1 (8.3%), –	–
Squire [18], 2012 (n = 21)	7 (33.3%) BNI I 17 (81%) BNI I–III 4/5 (80%) of VS 13/14 (92.8%) of M	–	–	12	–	BNI I–IIIb 1: 66% 2: 53%	–	2 (9.5%)
Tanaka [19], 2013 (n = 31)	18 (58%) BNI I	–	7/18 (38.9%)	–	7/18 BNI I (38.9%) 4 (13%) BNI III	BNI I–IIIb 0.5: 80% 1: 80% 2: 72%	–	5 (16.1%) overall 2 (6.73%) new or increased facial numbness 1 (3%) masseter weakness 1 (3%) abducens palsy 1 (3%) internal carotid artery occlusion with further stroke (meningioma of the cavernous sinus)
Chivukula [12], 2017 (n = 12)	6/10 (60%) after tumor targeting 6 (50%) BNI I after nerve targeting 10 (83.3%) BNI I–IIIb after nerve targeting	–	6/10 (60%)	41	–	–	1 (8.33%) MVD, 1 (8.33%) to REZ	3 (25%) facial sensory nerve dysfunction

Table 2 (continued)

First author [ref.], year	Patients experiencing an initial improvement	Time to pain relief, months	Patients with pain recurrence	Time to recurrence, months	Patients with a lasting response	Actuarial[a], years	Patients undergoing craniotomy after SRS, repeat SRS	Patients experiencing complications
Cho [13], 2016 (n = 50)	46 (92%) BNI I–IIIb	–	13/46 (28.3%)	–	18 (36%) BNI I	BNI I–IIIb 1: 73.5% 2: 70.7% 3: 76.5%	–	–
Kim [21], 2016 (n = 15)	14 (93.3%) BNI I–IIIb	5.5	3 (21.4%)	–	13 (86.7%) BNI I–IIIb	BNI I–IIIb 1: 93% 2: 83% 5: 69%	–	4 (26.7%)
Park [22], 2016 (n = 21)	7 (33.3%) BNI I 15 (71%) BNI I–IIIb after a single session with tumor targeting 21 (100%) after the second session with nerve targeting	–	6/15 (40%) after first session	40 (5–96) after first session	–	–	–	–

[a] As stated from the individual manuscripts in terms of probability of achieving durable response.

Maintenance of Pain Relief on a Long-Term Basis
Tumor shrinkage after SRS was not necessarily associated with a better clinical outcome, BNI I–IIIb [19].

Tumor Targeting Series
Maintenance of BNI I was reported in 42/129 cases, for a rate of 36.4% (range 20.1–52.7; $\wedge^2 = 75.8\%$, $p_{heterogeneity} = 0.002$, $p < 0.001$; Fig. 3a). Moreover, pain relief after SRS BNI I–IIIb was encountered in 29/70 cases, for a rate of 41.2% (range 29.8–52.7; $I^2 = 0\%$, $p_{heterogeneity} = 0.628$, $p < 0.001$; Fig. 3b).

Tumor and Nerve Targeting Series (in the Same Session or Separate Sessions)
Kim et al. [21] reported 13/15 (86.7%) BNI I–IIIb in their series.

Recurrence
Recurrence is described in 70/205 patients for series focusing on tumor targeting, for a rate of 34.7% (range 21.7–47.6; $I^2 = 76.86\%$, $p_{heterogeneity} < 0.001$, $p < 0.001$; Fig. 4a).

Complications
Complications were reported in 24/174 cases in series focusing on tumor targeting, for a rate of 12.6% (range 6.3–18.8; $I^2 = 35.95\%$, $p_{heterogeneity} = 0.154$, $p < 0.001$; Fig 4b). Kim et al. [21] reported 4/15 (26.7%) cases targeting both the tumor and the nerve.

Discussion

In the current literature, there is a gap of knowledge with regard to potential improvements in secondary TN related to meningiomas or VS. Here, we analyzed series independently of their targeting policy (i.e., the tumor itself vs. the tumor and the nerve vs. the nerve only). Pain relief after SRS was reported as BNI I in 50.5% (range 36–65.1%) and BNI I–IIIb in 83.8% (range 77.8–89.8%). There was no significant difference across series regarding the outcomes with tumor targeting and tumor and nerve targeting. Recurrence was described in 34.7% (range 21.7–47.6; tumor targeting). Maintenance of BNI I was reported in 36.4% (range 20.1–52.7) and maintenance of BNI I–IIIb in 41.2% (range 29.8–52.7; tumor targeting series). When both the nerve and tumor were targeted, 1 series reported BNI I–IIIb in 86.7% at the last follow-up. Complications were encountered in 12.6% (range 6.3–18.8%; tumor targeting series); however, the
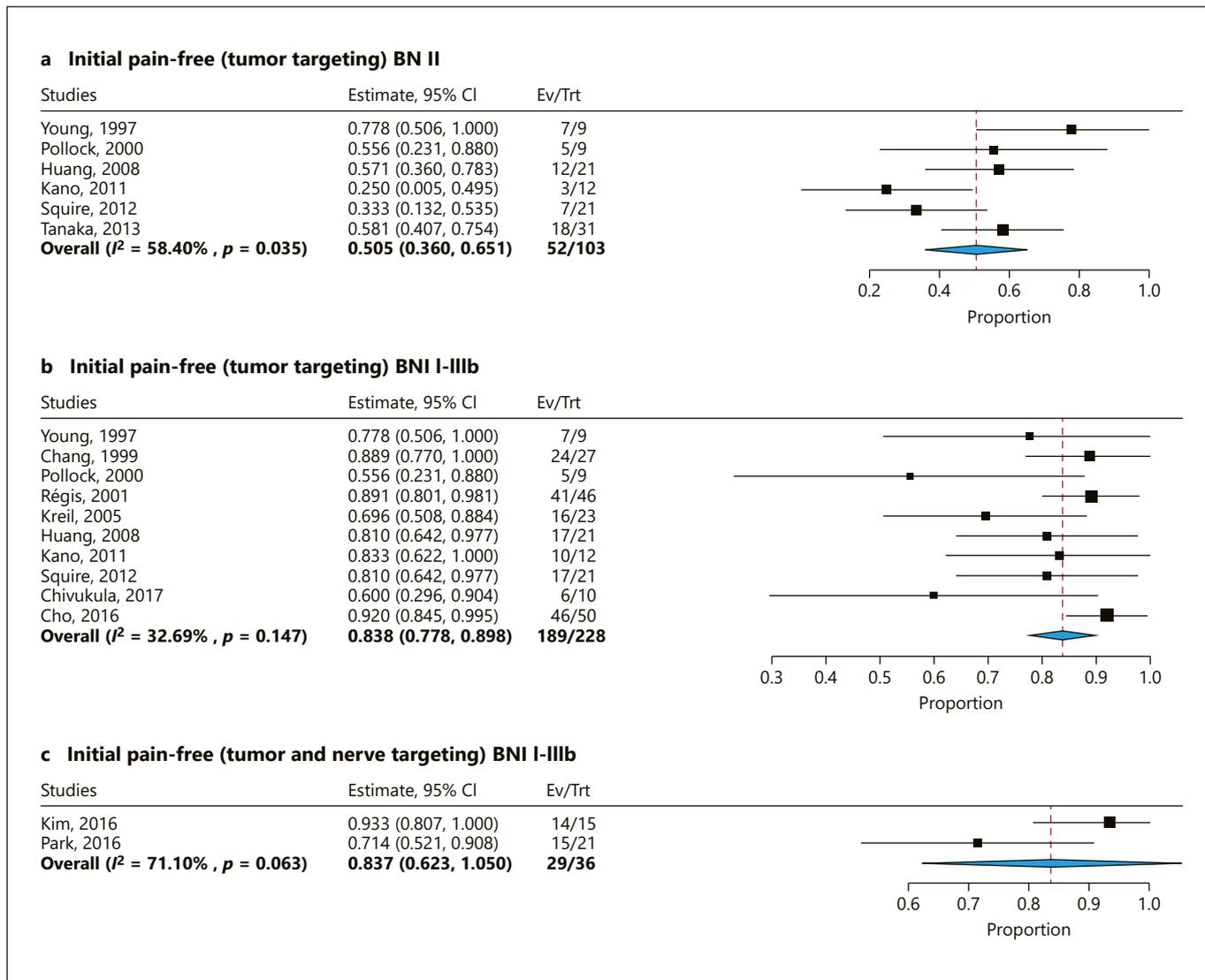
a Initial pain-free (tumor targeting) BN II

Studies	Estimate, 95% CI	Ev/Trt
Young, 1997	0.778 (0.506, 1.000)	7/9
Pollock, 2000	0.556 (0.231, 0.880)	5/9
Huang, 2008	0.571 (0.360, 0.783)	12/21
Kano, 2011	0.250 (0.005, 0.495)	3/12
Squire, 2012	0.333 (0.132, 0.535)	7/21
Tanaka, 2013	0.581 (0.407, 0.754)	18/31
Overall (I^2 = 58.40% , p = 0.035)	**0.505 (0.360, 0.651)**	**52/103**

b Initial pain-free (tumor targeting) BNI I-IIIb

Studies	Estimate, 95% CI	Ev/Trt
Young, 1997	0.778 (0.506, 1.000)	7/9
Chang, 1999	0.889 (0.770, 1.000)	24/27
Pollock, 2000	0.556 (0.231, 0.880)	5/9
Régis, 2001	0.891 (0.801, 0.981)	41/46
Kreil, 2005	0.696 (0.508, 0.884)	16/23
Huang, 2008	0.810 (0.642, 0.977)	17/21
Kano, 2011	0.833 (0.622, 1.000)	10/12
Squire, 2012	0.810 (0.642, 0.977)	17/21
Chivukula, 2017	0.600 (0.296, 0.904)	6/10
Cho, 2016	0.920 (0.845, 0.995)	46/50
Overall (I^2 = 32.69% , p = 0.147)	**0.838 (0.778, 0.898)**	**189/228**

c Initial pain-free (tumor and nerve targeting) BNI I-IIIb

Studies	Estimate, 95% CI	Ev/Trt
Kim, 2016	0.933 (0.807, 1.000)	14/15
Park, 2016	0.714 (0.521, 0.908)	15/21
Overall (I^2 = 71.10% , p = 0.063)	**0.837 (0.623, 1.050)**	**29/36**

Fig. 2. Pain relief after SRS. Tumor targeting: BNI I (**a**) and BNI I–IIIb (**b**). **c** Tumor and nerve targeting: BNI I–IIIb.

rate was much higher, at 26.7%, in the only series that reported them after targeting both the nerve and the tumor. The most common complication was facial numbness.

TN secondary to benign skull-base tumors is a specific case scenario. Of interest are both tumor control and symptomatic improvement. Microsurgical resection has the advantage of a decrease in both the tumor volume and the mass effect on the nerve. In tumor-related cases, Barker et al. [6] reported a series with a mean postoperative follow-up of 9 years, with frequent and long-lasting pain relief, i.e., complete, as high as 81% at 10 years after surgery, and partial, 4%. In the surgical series, new cranial nerve neuropathies were reported in 6.25–19.2% of cases [6, 8, 10]. In selected cases, SRS, and gamma knife surgery in particular, has been shown to be safe and effective in the long term in large cohorts of skull-base meningiomas [28–31] and VS [32–34].

With regard to the clinical aspects, several issues warrant further discussion. Bullitt et al. [7] suggested that the specific trigeminal site of the tumor influences symptoms and signs, i.e., tumors that are peripherally placed cause atypical TN, those in the middle fossa cause severe atypical TN, and those in the posterior fossa cause typical TN. The mechanism that generates pain is considered to be direct trigeminal root compression or vascu-
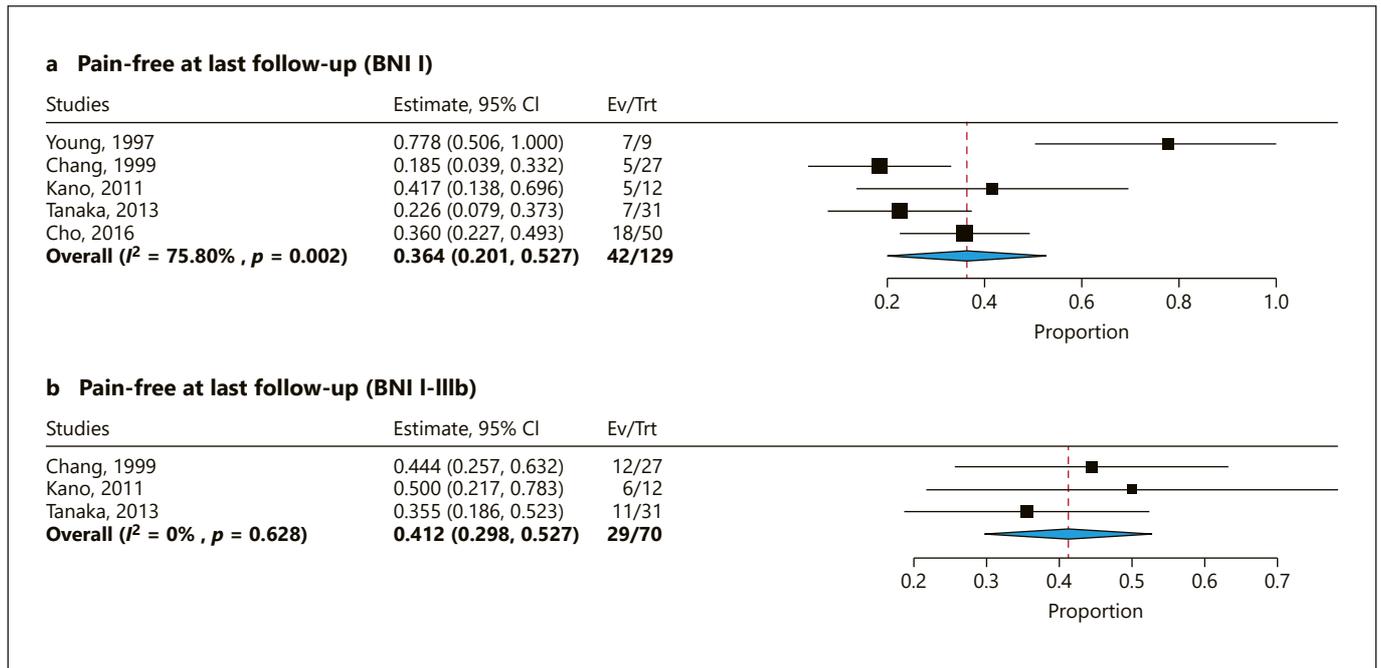
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Fig. 3. Pain-free at last follow-up (tumor targeting), BNI I (**a**) and BNI I–IIIb (**b**).

lar compression secondary to a displacement by the tumor [6].

While the tumor is the primary target, the mechanism of action of SRS in secondary TN remains largely undiscovered. However, Régis et al. [35] suggested that there are different mechanisms of action for the relief of secondary tumor-related facial pain by SRS, and they performed experimental studies to confirm this. Chang et al. [11] suggested that reduced abnormal electrical transmission might explain such changes. Huang et al. [14] suggested that the volume of demyelination of the nerves in tumors is probably higher than in idiopathic TN, as is the volume of radiation during treatment. Thus, the dose threshold for pain relief may be lower in the tumor condition. In fact, the maximum dose prescribed for idiopathic TN (70–90 Gy) is much higher [4, 5] than that prescribed for tumors (26–32 Gy) [28, 29]. Some authors include neuropathic pain cases, and report that patients are not responsive to SRS [17].

An open question is whether tumor response, particularly tumor decrease, after SRS is linked with alleviating TN. Chang et al. [11] reported 1 case in which pain disappeared and 3 cases with pain reduction in a series of 27 cases, even though there were no changes in tumor volume during follow-up. Huang et al. [14] suggested that tumor shrinkage may help with the relief of tic doulou-

reux. In sum, tumor shrinkage was associated with pain relief in some of the series [14], while other authors did not find any associations [15]. Some series suggested that pain recurs more often in patients with meningiomas than in those with VS [13].

Overall, complications were rare. The most common complication was facial numbness. Beside numbness, Chang et al. [11] reported transient tinnitus and diminished hearing (in the VS context). Interestingly, there were no cases reported of corneal anesthesia or anesthesia dolorosa. Other complications included balance problems [18], masseter weakness [19], abducens palsy [19], and ipsilateral hemispheric stroke [19]. Kim et al. [21] reported a series of single-session SRS targeting of both nerve and tumor, with no further facial weakness, altered taste function, or hearing and balance difficulties. Of note, hearing loss seems to be encountered more with VS than with meningiomas of the skull-base, as reported in recent studies [36, 37].

In the near future, treatment should be tailored to a patient's specific needs, as suggested by other groups using SRS (Cyberknife, Accuray) which have reported their algorithm in dealing with tumor-related facial pain, e.g., the Stanford group, using a dose regimen of 18–21 Gy in 3 fractions [38]. Specific issues remain to be developed by further studies: local control might not necessarily im-
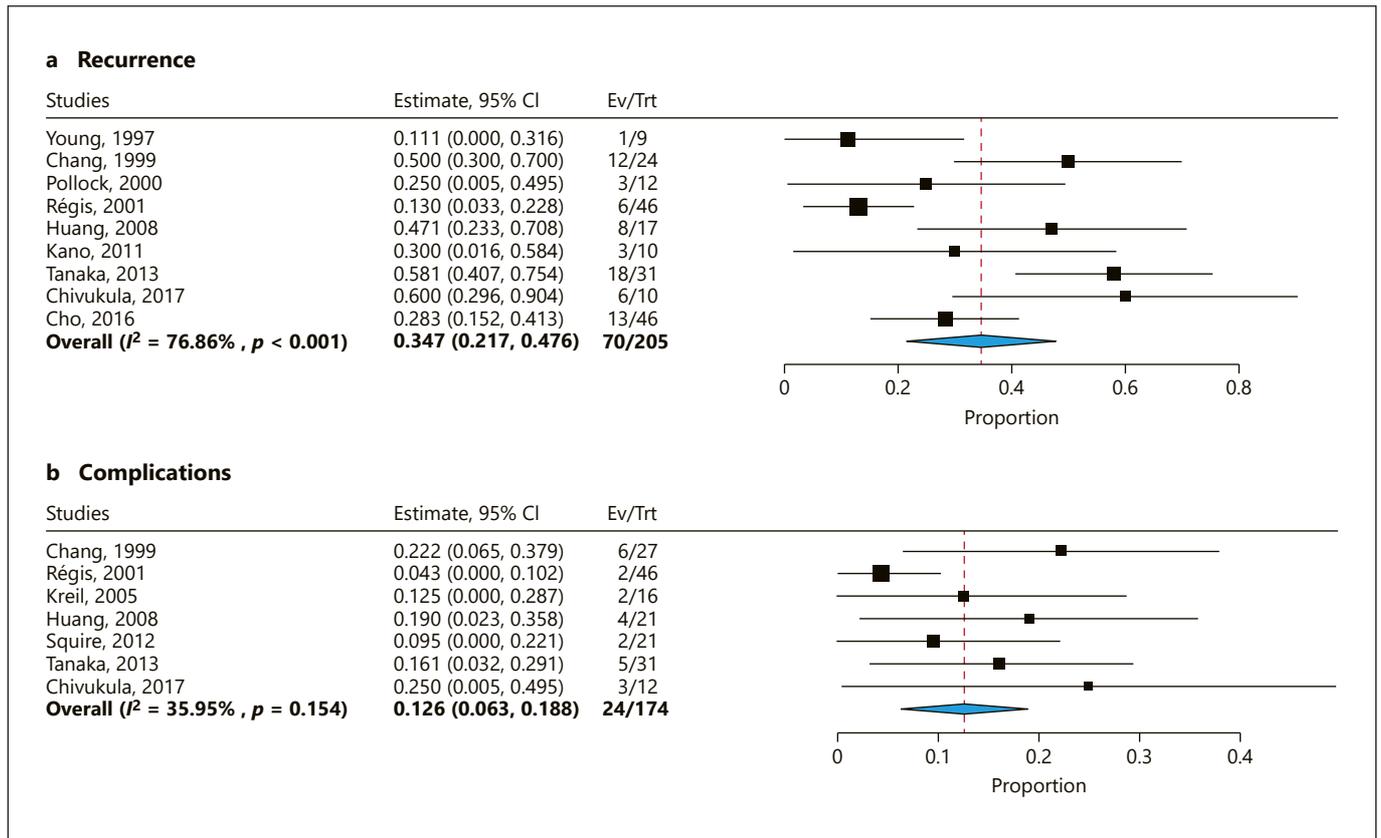
a Recurrence

Studies	Estimate, 95% CI	Ev/Trt
Young, 1997	0.111 (0.000, 0.316)	1/9
Chang, 1999	0.500 (0.300, 0.700)	12/24
Pollock, 2000	0.250 (0.005, 0.495)	3/12
Régis, 2001	0.130 (0.033, 0.228)	6/46
Huang, 2008	0.471 (0.233, 0.708)	8/17
Kano, 2011	0.300 (0.016, 0.584)	3/10
Tanaka, 2013	0.581 (0.407, 0.754)	18/31
Chivukula, 2017	0.600 (0.296, 0.904)	6/10
Cho, 2016	0.283 (0.152, 0.413)	13/46
Overall (I^2 = 76.86% , p < 0.001)	**0.347 (0.217, 0.476)**	**70/205**

b Complications

Studies	Estimate, 95% CI	Ev/Trt
Chang, 1999	0.222 (0.065, 0.379)	6/27
Régis, 2001	0.043 (0.000, 0.102)	2/46
Kreil, 2005	0.125 (0.000, 0.287)	2/16
Huang, 2008	0.190 (0.023, 0.358)	4/21
Squire, 2012	0.095 (0.000, 0.221)	2/21
Tanaka, 2013	0.161 (0.032, 0.291)	5/31
Chivukula, 2017	0.250 (0.005, 0.495)	3/12
Overall (I^2 = 35.95% , p = 0.154)	**0.126 (0.063, 0.188)**	**24/174**

Fig. 4. a Recurrence. **b** Complications.

prove symptomatology, pain relief might occur after a latency period, and benign tumors respond slow to irradiation.

The most difficult question to answer, from currently available data, is: What is the appropriate target? Moreover, should this be followed by a second targeting, in the same session, or a long time after the first? Would a boost to the nerve be necessary if the tumor is the target?

This analysis had some limitations. The first is the retrospective nature of the included series. The second is related to the fact that some reports included other pathologies besides meningiomas and VS, although in a minor proportion; this might have influenced some of the outcomes. The third is that not all the authors used the BNI or other standard scales for reporting. The fourth is that several studies included malignant or biologically aggressive cases. The fifth, which applies to all TN studies, was the examination of the final outcome, which should be based on clinical examinations rather than telephone interviews. The sixth is that preoperative analysis re-

vealed neuropathic pain in some of the cases. The seventh is related to the imbalance in the number of patients undergoing the different targeting techniques, with a particularly a low number of cases in which both the nerve and tumor were targeted.

Conclusions

SRS for benign tumors, such as meningiomas and VS, is associated with favorable clinical outcomes, although not as much as SRS for idiopathic TN. The current literature illustrates heterogeneity in targeting policy and reporting of the results.

Though targeting both the nerve and the tumor seems to achieve better long-term results, the rate of complications is much higher and the number of patients treated is limited. Future reports should focus on potential randomization between different targeting techniques and uniformity in reporting the results.

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Statement of Ethics

The research presented here was conducted in accordance with the World Medical Association Declaration of Helsinki, the appropriate guidelines for human studies, and animal welfare regulations including the Animal Research: Reporting of in vivo Experiments (ARRIVE) guidelines. It was approved by the appropriate institutional review bodies. For this type of study, formal ethics committee approval is not necessary.

Conflict of Interest Statement

C.T. is a scientific advisor for Elekta Instruments, AB, Sweden, but with no relation to this paper. The other authors report no conflicts of interest.

Author Contributions

Each author (1) made substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work; (2) participated in drafting the work or revising it critically for important intellectual content; (3) approved the final version to be published; and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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