

Stereotactic radiosurgery for trigeminal neuralgia: a systematic review

International Stereotactic Radiosurgery Society practice guidelines

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OBJECTIVES The aims of this systematic review are to provide an objective summary of the published literature specific to the treatment of classical trigeminal neuralgia with stereotactic radiosurgery (RS) and to develop consensus guideline recommendations for the use of RS, as endorsed by the International Society of Stereotactic Radiosurgery (ISRS).

METHODS The authors performed a systematic review of the English-language literature from 1951 up to December 2015 using the Embase, PubMed, and MEDLINE databases. The following MeSH terms were used in a title and abstract screening: "radiosurgery" AND "trigeminal." Of the 585 initial results obtained, the authors performed a full text screening of 185 studies and ultimately found 65 eligible studies. Guideline recommendations were based on level of evidence and level of consensus, the latter predefined as at least 85% agreement among the ISRS guideline committee members.

RESULTS The results for 65 studies (6461 patients) are reported: 45 Gamma Knife RS (GKS) studies (5687 patients [88%]), 11 linear accelerator (LINAC) RS studies (511 patients [8%]), and 9 CyberKnife RS (CKR) studies (263 patients [4%]). With the exception of one prospective study, all studies were retrospective.

The mean maximal doses were 71.1–90.1 Gy (prescribed at the 100% isodose line) for GKS, 83.3 Gy for LINAC, and 64.3–80.5 Gy for CKR (the latter two prescribed at the 80% or 90% isodose lines, respectively). The ranges of maximal doses were as follows: 60–97 Gy for GKS, 50–90 Gy for LINAC, and 66–90 Gy for CKR.

Actuarial initial freedom from pain (FFP) without medication ranged from 28.6% to 100% (mean 53.1%, median 52.1%) for GKS, from 17.3% to 76% (mean 49.3%, median 43.2%) for LINAC, and from 40% to 72% (mean 56.3%, median 58%) for CKR. Specific to hypesthesia, the crude rates (all Barrow Neurological Institute Pain Intensity Scale scores included) ranged from 0% to 68.8% (mean 21.7%, median 19%) for GKS, from 11.4% to 49.7% (mean 27.6%, median 28.5%) for LINAC, and from 11.8% to 51.2% (mean 29.1%, median 18.7%) for CKR. Other complications included dysesthesias, paresthesias, dry eye, deafferentation pain, and keratitis. Hypesthesia and paresthesia occurred as complications only

ABBREVIATIONS BMC = balloon microcompression; BNI = Barrow Neurological Institute; CKR = CyberKnife radiosurgery; DVH = dose-volume histogram; FFP = freedom from pain; GKS = Gamma Knife surgery; HSRT = hypofractionated stereotactic radiotherapy; ISRS = International Society of Stereotactic Radiosurgery; LINAC = linear accelerator; MVD = microvascular decompression; QOL = quality of life; RCT = randomized controlled trial; REZ = root entry zone; RFT = radiofrequency thermocoagulation; RS = radiosurgery; SCA = superior cerebellar artery; TN = trigeminal neuralgia; TTPR = time to pain relief.

SUBMITTED March 2, 2017. **ACCEPTED** September 11, 2017.

INCLUDE WHEN CITING Published online April 27, 2018; DOI: 10.3171/2017.9.JNS17545.

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when the anterior retrogasserian portion of the trigeminal nerve was targeted, whereas the other listed complications occurred when the root entry zone was targeted. Recurrence rates ranged from 0% to 52.2% (mean 24.6%, median 23%) for GKS, from 19% to 63% (mean 32.2%, median 29%) for LINAC, and from 15.8% to 33% (mean 25.8%, median 27.2%) for CKR. Two GKS series reported 30% and 45.3% of patients who were pain free without medication at 10 years.

CONCLUSIONS The literature is limited in its level of evidence, with only one comparative randomized trial (1 vs 2 isocenters) reported to date. At present, one can conclude that RS is a safe and effective therapy for drug-resistant trigeminal neuralgia. A number of consensus statements have been made and endorsed by the ISRS.

<https://thejns.org/doi/abs/10.3171/2017.9.JNS17545>

KEYWORDS trigeminal neuralgia; systematic review; functional neurosurgery; stereotactic radiosurgery; pain

TRIGEMINAL neuralgia (TN), referred to as “tic douloureux” by the French neurosurgeon André,⁵ is a severe, unilateral, lancinating, and electric-like facial pain. It remains the most common neuralgia but with a low global incidence of 4–5 cases per 100,000 persons. Diagnosis of this condition is made mainly on a clinical basis given the classic signs and symptoms of paroxysmal attacks with an abrupt onset, a duration of seconds to 2 minutes, periods of spontaneous remission, the presence of “trigger zones,” no objective neurological deficit, no other identified causes of facial pain, the most common distribution along the second or third division of the trigeminal nerve, and an initial response to carbamazepine.⁴⁵

The leading pathophysiological hypothesis specific to idiopathic TN describes demyelination of trigeminal sensory fibers within the proximal nerve root.⁷⁹ According to the preliminary findings of Walter Dandy,²³ which were confirmed decades later, most patients (80%–90%) present with an overlying blood vessel causing neurovascular compression at the root entry zone (REZ).¹¹ The vessel most frequently involved is the superior cerebellar artery (SCA), but veins can also contribute to this phenomenon.¹¹

Classification of TN as established by the International Headache Society⁴⁵ includes classical and symptomatic. “Classical TN” refers to all cases without an established etiology (idiopathic), including those with potential vascular compression. Symptomatic TN is often caused by a tumor, multiple sclerosis, or skull-base structural abnormalities.⁴⁵ Patients with a suspected diagnosis of TN should undergo brain MRI to better visualize the trigeminal nerve and the eventual offending vessel but also to exclude secondary cases of TN in the context of a tumor, demyelinating disease, vascular malformations, and so forth.

The first therapeutic line is pharmacological with carbamazepine. Initial effectiveness has been reported in nearly 90% of patients⁵² and is the only antiepileptic drug shown in randomized controlled trials (RCTs) to reduce both the intensity and frequency of attacks.¹³⁹ Nevertheless, due to the induction of hepatic enzymes, which metabolize the drug, its efficacy can decrease or even decline completely after a period of stability at a given dose, and higher doses can become necessary. Additionally, patients can develop a large spectrum of side effects, some interfering strongly with quality of life (QOL).

The second therapeutic line is surgical and is reserved for patients with medically intractable pain or those who present with side effects related to medication. The 3 main surgical techniques include microvascular decompression

(MVD), percutaneous procedures (balloon microcompression [BMC], glycerol injection, radiofrequency thermocoagulation [RFT]), and external beam stereotactic radiosurgery (RS).

Microvascular decompression, pioneered by Peter Jannetta, is considered the reference technique as it addresses the underlying cause, that is, neurovascular compression.⁵⁰ Although the procedure offers rapid improvement, probably because of the immediate setback of the underlying distortion and compression of demyelinated axons, major complications of the surgery can include death, brainstem infarction, ipsilateral hearing loss, CSF leakage, and so forth.^{11,50} What is less clear is the extent to which normal remyelination occurs over the long term to contribute to the resolution of the pathological axonal arrangement.⁷⁹ Percutaneous procedures are also effective, considered to be ablative techniques and mechanically based on physical (BMC), thermic (RFT), or chemical (glycerol injection) action at the level of the gasserian ganglion. There are no RCTs comparing the outcomes of these types of interventions, but all are considered ablative procedures given their high risk of producing dysesthesias, corneal keratitis, or severe facial numbness.

In 1951 the concept of RS was introduced by the Swedish neurosurgeon Lars Leksell, who treated a TN patient using a prototype guiding device linked to a dental x-ray machine. Essentially a “stereotactic gangliotomy”⁶⁹ was performed, similar to the concept of a percutaneous technique. As external beam technology and neuroimaging evolved, technologies such as the Gamma Knife, linear accelerator (LINAC), and CyberKnife RS (CKR) developed. The main principle of RS, regardless of the technique, is to target the trigeminal nerve with high precision, in a single session, based on high-resolution MRI and CT studies. With the evolution of neuroimaging came refinement in the technique and the target. Several large Gamma Knife surgery (GKS) series have already advocated for the safety and efficacy of RS, in particular, by reporting long-term and very-long-term results.^{63,110,114,115,144} Additionally, a small number of studies have reported outcomes for the other RS techniques, including the LINAC and CKR, though with a more limited number of patients and follow-up periods.^{1,12,31,102,119,124,125,129,138}

The aims of this systematic review are to provide an objective summary of the published literature specific to the treatment of TN with RS and to develop consensus guideline recommendations for the use of RS, as endorsed by the International Society of Stereotactic Radiosurgery (ISRS).

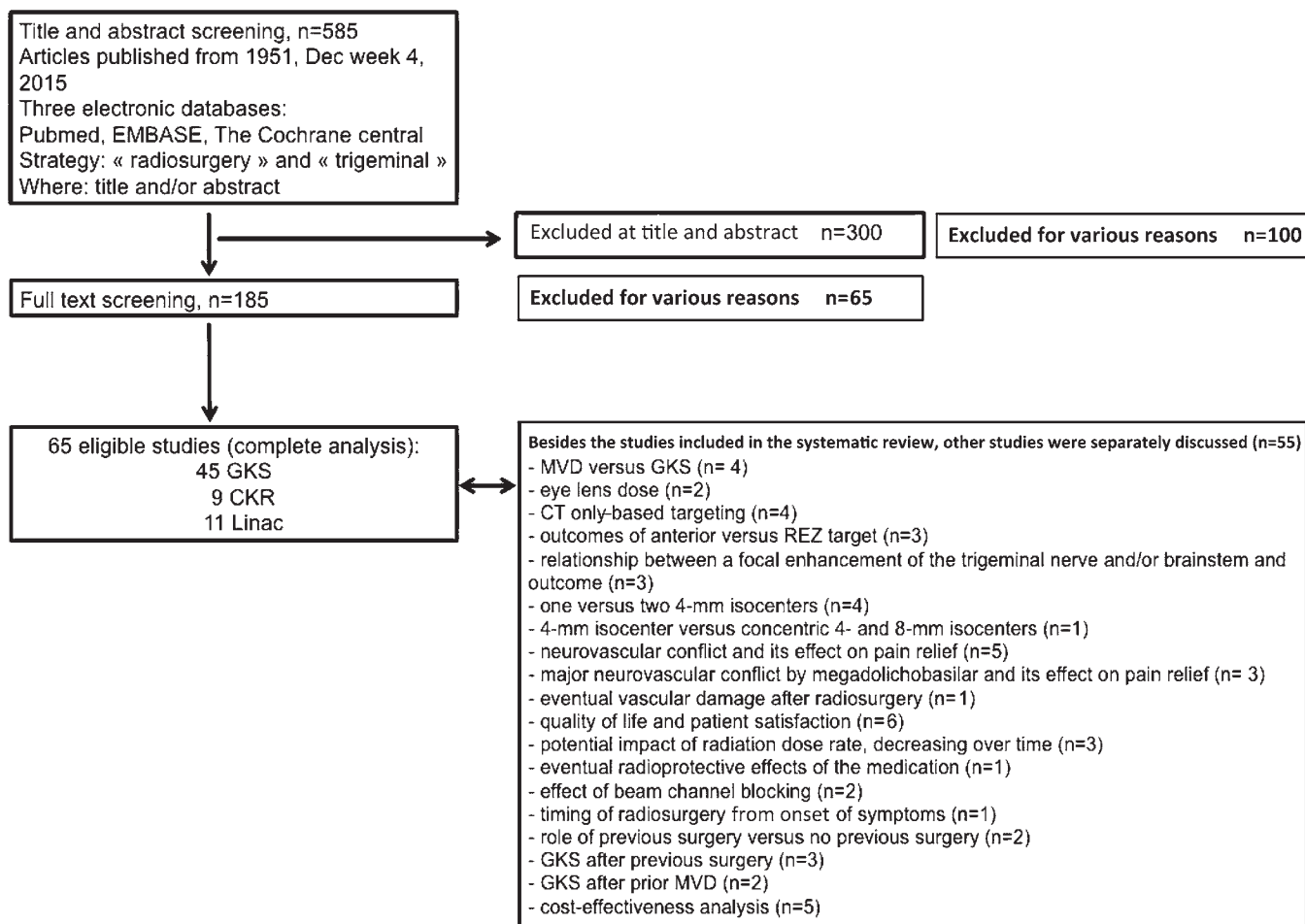


FIG. 1. Flow chart to final number of eligible studies.

Methods

Search Method

A systematic review of the English-language literature from 1951–December 2015 was performed using the MEDLINE, Embase, and PubMed databases. The following search terms were used in a screening of titles and/or abstracts: “radiosurgery” AND “trigeminal.”

Inclusion Criteria and Identified Studies

Inclusion criteria were as follows: articles (prospective and retrospective studies) written in the English language and reporting on outcomes specific to external beam radiosurgical treatments of classical idiopathic TN, the first RS treatment, MRI-based targeting (CT-based targeting reported separately to exclude potential bias), and clear outcomes obtained using validated instruments. Conversely, exclusion criteria were studies that did not report specific outcomes for idiopathic TN and those reporting on repeat RS or RS in the treatment of TN associated with multiple sclerosis or other secondary causes. Duplicate studies were defined as those including outcomes on a previously reported population; however, if the study included additional patients and more follow-up data that were sepa-

rately described, that new information was included. Five hundred eighty-five studies were initially identified (Fig. 1), and 300 were excluded at the title and abstract screening because they did not meet inclusion criteria. From the remaining 285 studies, 100 were excluded for various reasons. One hundred eighty-five studies were subjected to a full-text review, 65 of which did not meet inclusion criteria, leaving 120 studies for subsequent analysis. Sixty-five of these 120 studies were considered relevant to the present review, and the remaining 55 papers were also reviewed and are discussed separately as they deal with specific aspects that need to be discussed in the context of TN (Fig. 1).

Reporting Results

Results are reported for the 65 studies (6461 patients): 45 GKS studies (5687 patients [88%]),^{8,9,17,21,24,25,27,28,43,44,49,53,57,59,61–63,66,67,74,76,77,80,82,83,85,89,90,98,100,103,106,111,112,114,117,118,120,111,132,146,137,144,145,149} 11 LINAC RS studies (511 patients [8%]),^{18,19,26,39,42,64,108,116,124,125,146} and 9 CKR RS studies (263 patients [4%])^{1,31,65,72,102,119,126,129,138} (Table 1). With the exception of 1 prospective study by Régis et al.,¹¹² all other studies were retrospective.

TABLE 1. Summary of studies included in this systematic review

Authors & Year	No. of Cases	Mean Age in Yrs (range)	Mean or Median FU (mos)	FU Range (mos)	Mean or Median Dose in Gy	Maximal Dose in Gy	Target in Relation to REZ (mm)
GKS studies							
Régis et al., 1995	20	75 (59–83)	11†	3–18	84*/90†	70–90	7–8
Kondziolka et al., 1996 ⁵⁹	51	64 (21–89)	9.6*	2–29	—	60–90	2–4
Kondziolka et al., 1996 ⁶¹	50	—	19†	11–36	71.1*	60–90	—
Young et al., 1997	51	—	16.3*	6–36	—	—	0
Kondziolka et al., 1998	106	67 (32–92)	18†	6–48	75.9*/80†	70–90	2–4
Kannan et al., 1999	6	56 (42–79)	—	5–16	75.7*/80†	70–80	2–4
Chang et al., 2000	15	63.8 (38.7–82.2)	7.1*	3.9–23.7	76.3*	70–80	—
Rogers et al., 2000	54	67 (43–89)	12†	3–28	70†	70–80	—
Maesawa et al., 2001	220	70 (26–92)	22†	1–78	80†	60–90	2–4
Zheng et al., 2001	80	67 (32–92)	23.7*	12–43	75.6*	70–90	4–6
Matsuda et al., 2002	41	—	13*	3–36	80†	80	0
Pollock et al., 2002	117	67.8	26†	1–48	82.6*	70–90	—
Petit et al., 2003	112	64 (24–95)	30†	8–66	—	70–80	2–4
Shaya et al., 2004	40	64.3 (39–82)	14†	3–31	80*	70–90	2–4
Massager et al., 2004	47	69 (35–86)	16*	6–42	90†	90	7–8
Cheuk et al., 2004	112	62.02 (24–96)	—	—	75†	60–80	2–4
Drzymala et al., 2005	73	69 (34–100)	13.7†	1.3–44.7	87†	76–98	0
McNatt et al., 2005	49	68 (38–87)	44*	12–70	80*	80	0
Sheehan et al., 2005	136	68 (22–90)	19†	2–96	80†	50–90	2–4
Tawk et al., 2005	38	70 (29–88)	24†	6–27	80.5*/80†	70–90	0
Urgosik et al., 2005	107	75 (45–91)	60†	12–96	76.6*/80†	70–80	0
Régis et al., 2006	100	67.5 (29–90)	—	—	85†	70–90	7.8
Longhi et al., 2007	170	63.4 (23–89)	37.4*	6–144	85*	75–95	2–5
Little et al., 2008	185	69 (57–81)	75.6*	48–126	80†	70–90	0
Huang et al., 2008 ⁴⁹	89	63.2 (34–85)	68*	32–104	78.8*	60–90	0
Dellaretti et al., 2008	76	64 (27–83)	20.3*	6–42	85.1*	75–90	7–8
Azar et al., 2009	30	55 (31–80)	—	—	90.1*/90†	85–95	2–4
Han et al., 2009	62	61 (50–73)	58*	16–107	79.7*	75–80	2–4
Dhople et al., 2009	112	64 (24–96)	67.2†	13–115	75†	70–80	0
Riesenburg et al., 2010	53	65.8 (38–94)	48*	36–66	80.6*/80†	75–90	0 (72%) & Meckel's cave (28%)
Verheul et al., 2010	450	65 (27–91)	28†	3–85	80*	80	0
Kondziolka et al., 2010	503	72 (26–95)	24†	3–156	80†	60–90	2–4
Park et al., 2011 ¹⁰⁰	62	62.7 (51.4–74)	76.4†	12–161	82.4*/85†	68–90	0
Loescher et al., 2012	72	65.6	—	—	80*	80	0
Hayashi et al., 2011	130	68 (31–88)	38*	24–66	—	—	7–8
Park & Hwang, 2011	17	62.7 (41–82)	43.8*	36–59	80*	80–90	2–4
Lee et al., 2012	40	61.5 (25–84)	92*	60–144	77.1*	65.2–83.6	0
Marshall et al., 2012	448	67 (22–92)	20.9*	3–86	88*/90†	80–97	2–4
Elaimy et al., 2012	108	67 (22–94)	15†	—	86†	70–90	0
Young et al., 2013	315	70.8 (52.9–84.1)	68.9*	27.1–110.7	90†	90	2–4
Lee et al., 2013	91	—	—	24–90	88*	75–90	7–8
Aykol et al., 2014	93	57.06 (18–87)	57.1*	12–84	80.38*	70–90	0
Karam et al., 2014	36	71 (29–97)	36†	—	90†	80–90	0
Lucas et al., 2014	446	67.5 (56.6–75.8)	21.2†	9.7–43	88.06*/90†	80–97	Retrogasserian
Régis et al., 2016 ¹¹⁴	497	68.3 (28.1–93.2)	43.8†	12–174.4	85†	70–90	7.6
CKR studies							
Romanelli et al., 2003	10	—	—	—	64.3*	66–70	3

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TABLE 1. Summary of studies included in this systematic review

Authors & Year	No. of Cases	Mean Age in Yrs (range)	Mean or Median FU (mos)	FU Range (mos)	Mean or Median Dose in Gy	Maximal Dose in Gy	Target in Relation to REZ (mm)
CKR studies (continued)							
Lim et al., 2005	41	68	11*	6–15	70.7*	—	2–3
Villavicencio et al., 2008	95	69.8	22†	12–46	78†	70–85.4	2–3
Fariselli et al., 2009	33	74	23†	9–37	—	—	2–3
Adler et al., 2009	46	78	10.5*	6–29	73.5*	—	2–3
Lazzara et al., 2013	17	69.4	11.8*	1–27	73.06*	72.91–73.73	2–3
Tang et al., 2011	16	67.8	20.4*	6–32	80.5*	75–86.5	3
Peddada et al., 2011	1	74	—	—	—	—	2–3
Soboleva et al., 2012	4	63	8*	—	—	70–90	—
LINAC studies							
Goss et al., 2003	25	65 (50–84)	18*	8–52	90†	90	0
Smith et al., 2003	60	66.1	23†	2–70	83.3*	70–90	0
Frighetto et al., 2004	22	—	21.2*	8–52	90†	75–90	0
Kubicek et al., 2004	20	58 (40–81)	56.5*	—	—	82.3–100	0
Chen et al., 2004	44	65	15†	—	—	90	0
Richards et al., 2005	28	74 (44–88)	12†	1–40	80†	80	0
Pusztaszeri et al., 2007	17	71 (48–77)	12†	1–60	—	50–56	0
Zahra et al., 2009	20	—	14.2†	—	—	90	0
Chen et al., 2010	44	65 (32.2–90.5)	15†	—	90†	90	0
Dos Santos et al., 2011	52	—	26.6†	6.3–99.9	—	50–80	Gasserian/cisternal
Smith et al., 2011	179	74 (32–90)	26.6†	5–89	—	70–90	0

— = not available; FU = follow-up.

* Mean value.

† Median value.

In addition to those studies selected for the systematic review, we separately discuss trials that considered MVD versus RS (4 studies);^{73,92,94,107} eye lens dose (2);^{70,81} CT only-based targeting (4);^{77,91,96,140} anterior versus REZ target (3);^{88,99,141} the relationship between focal enhancement of the trigeminal nerve and/or brainstem and outcome (3);^{2,38,40} one versus two 4-mm isocenters (4);^{4,26,32,106} one 4-mm isocenter versus concentric 4- and 8-mm isocenters (1);⁵⁴ the neurovascular conflict and its effect on pain relief (5);^{14,30,85,120,122} major neurovascular conflict by the megalodolichobasilar artery (3);^{97,127,135} eventual vascular damage after RS (1);⁷⁸ QOL and patient satisfaction (6);^{9,51,95,103,112,115} potential impact of radiation dose rate (3);^{6,10,68} eventual radioprotective effects of medication (1);³³ effect of beam channel blocking, with a longer irradiated nerve and integral dose (2);^{86,87} timing of RS from the onset of symptoms (1);⁹¹ previous surgery versus no previous surgery (2);^{34,35} GKS after previous surgery (3);^{49,57,77} GKS after prior MVD (2);^{75,133} and cost-effectiveness analysis (5).^{37,46,105,123,131}

Outcome Measures

Most of the studies reported outcomes using the Barrow Neurological Institute (BNI) Pain Intensity Scale or a variation: I, complete pain relief without medication; II, occasional pain not requiring medication; III, some pain

but adequately controlled with medications; IV, some pain inadequately controlled with medication; V, continued severe pain or no pain relief.¹¹⁸ Other studies used the classification proposed by Eller et al.,²⁹ which refers to idiopathic TN types 1 and 2. Trigeminal neuralgia type 1 (TN1) is described as typically sharp, shooting, electrical shock-like, episodic pain that is present more than 50% of the time but with pain-free intervals between attacks; TN2 is described as an aching, throbbing, or burning pain that is present more than 50% of the time but is constant in nature (constant background pain being the most significant attribute). The published data are confusing in some instances because some studies include patients with atypical pain and do not always describe it separately.

Recommendations Based on Agreement

Recommendations have been summarized based on the level of evidence (Table 2). Recommended statements were evaluated through a modified Delphi approach. The 2014 ISRS Board (all authors on these guidelines) independently rated their agreement with each recommendation on a 5-point scale (strongly agree, agree, disagree, strongly disagree, or uncertain). A prespecified threshold of 85% or more agreement (agree or strongly agree responses) represented consensus.

TABLE 2. Levels of evidence

Level	Description
I	Evidence from 1 or more well-designed, randomized controlled clinical trials, including overviews of such trials
II	Evidence from 1 or more well-designed comparative clinical studies such as nonrandomized cohort studies, case-control studies, and other comparable studies, including less well-designed RCTs
III	Evidence from case series, comparative studies with historical controls, case reports, and expert opinion, as well as significantly flawed RCTs

Data Analysis

For all nonrandomized studies, the generic inverse variance method and fixed effects model in Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) were used to pool data. The outcome measures used the log hazard ratio (lnHR) and its variance, which were estimated using the hazard ratio meta-analysis toolbox.¹⁰¹

Results

Follow-Up Periods

The mean and median follow-up periods for GKS ranged from 7.1 to 92 months and from 6.7 to 76 months (range 0–174.4 months), respectively. For LINAC studies, they ranged from 18 to 56.5 months and from 12 to 26.6 months (range 1–99.9 months), respectively. For CKR studies, they ranged from 8 to 20.4 months and from 22 to 23 months (range 1–46 months), respectively.

Radiosurgical Procedure: Mask or Frame Application and MRI Sequences

Gamma Knife surgery uses stereotactic head frame immobilization and is considered the gold standard of RS for TN.¹¹³ After application of a local anesthetic, the Leksell stereotactic G frame (Elekta Instruments AB) is fixed on the patient's head so that the frame is parallel to the intracisternal part of the fifth cranial nerve, which can be accomplished by corresponding the plane of the frame base to the orbitomeatal plane. The projection of the trigeminal incisura of the petrous bone can be localized 1.5 cm anterior and 1.5 cm superior to the external auditory meatus. The trigeminal incisura is positioned close to the center of the y-axis with appropriate adjustment in the z-axis.

Linear accelerator-based systems utilize stereotactic head frame immobilization or a facial mask with image guidance. In the vast majority of studies, a spherical dose distribution is delivered by 5–7 noncoplanar arcs through a circular collimator (4–5 mm).⁴¹

The CKR treatment requires facial mask immobilization, and the radiation dose is delivered by an X-band LINAC mounted on a robotic arm and guided by real-time imaging-assisted target tracking. The CKR dose plan is prepared using a CT scan that is fused with an MR image

for delineation of the nerve and brainstem. A 5- or 7.5-mm cone and trigeminal node set, which has a shorter source-to-axis distance, is used.³¹

With respect to imaging for treatment planning, T1-weighted with and/or without the injection of gadolinium and T2 constructive interference in steady state (CISS)/fast imaging employing steady state acquisition (FIESTA) sequences are used.^{31,41,63,113,114} In certain GKS centers, a CT scan supplements the neuroradiological examination. Targeting based solely on CT is discussed separately (see *Discussion, Targeting the Trigeminal Nerve Based Only on CT Images*).

Radiosurgical Procedure: Dose Selection and Target

Dose Selection

The mean maximal doses ranged from 71.1 to 90.1 Gy (prescribed at the 100% isodose line) for the GKS studies, from 70 to 90 Gy for LINAC studies, and from 64.3 to 80.5 Gy for CKR studies (the latter two prescribed at the 80% or 90% isodose lines, respectively; Table 1). The ranges of maximal doses were as follows: 60–97 Gy (large majority 60–90 Gy, more being rather exceptional) for GKS, 50–90 Gy for LINAC, and 66–90 Gy for CKR.

Target Selection

The anterior cisternal target has been used by Rand et al.,¹⁰⁹ Régis et al.,^{112,114,115,134} Dellaretti et al.,²⁴ Lucas et al.,⁸⁰ and Massager et al.⁸⁵ Otherwise, the REZ has been the most consistent target (Table 1 and Fig. 2).^{63,106}

Outcomes

Pain Relief Response and Time Points

The freedom from pain (FFP) response with or without medication adjustment is summarized as follows (mean and median [range]): GKS, 84.8% and 85.6% (66.6%–100%); LINAC, 87.3% and 88.5% (75%–100%); and CKR, 79.3% and 79% (50%–100%; Table 3). The difference in the FFP response between GKS and LINAC-based RS treatment was not statistically significant ($p = 0.4$, 2-sample t-test), with a difference of -2.5% between the means. Neither was there a statistically significant difference between GKS and CKR ($p = 0.42$, 2-sample t-test), with a difference of 5.4% between the means.

The FFP response without medication was as follows (mean and median [range]): GKS, 53.1% and 52.1% (28.6%–100%); LINAC, 49.3% and 43.2% (17.3%–76%); and CKR, 56.3% and 58% (40%–72%). The difference in the FFP response between GKS and LINAC was not statistically significant ($p = 0.54$, 2-sample t-test), with a difference of 3.8% between the means. Neither was there a statistically significant difference between GKS and CKR ($p = 0.64$, 2-sample t-test), with a difference of -3.1% between the means.

The times to pain relief (TTPRs) were as follows: the mean and median ranged from 15 to 78 days and from 10 to 90 days, respectively, for GKS; and from 28 to 81 days and from 8.5 to 60 days, respectively, for LINAC. The mean and median were not reported for the CKR studies.

The range intervals for TTPR varied from 0 to 480 days (all studies included), with most authors of the stud-

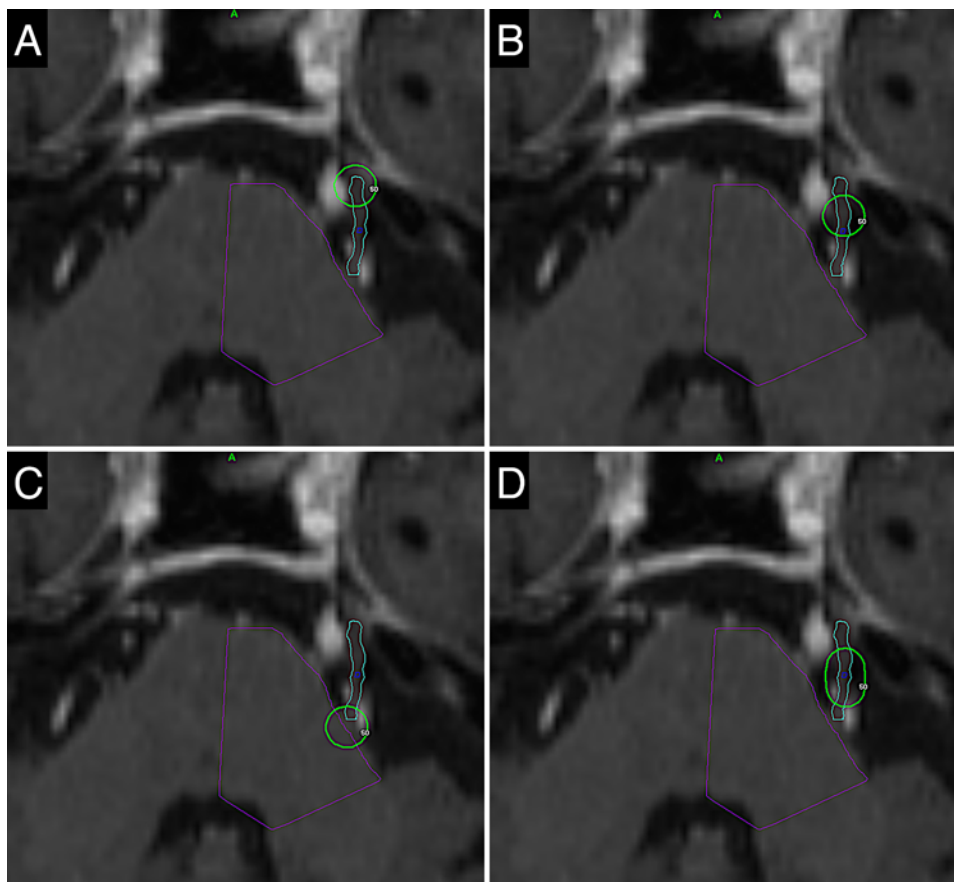


FIG. 2. Examples of different types of targeting (simulation), including the plexus triangularis (**A**), retrogasserian portion (far anterior cisternal, **B**), REZ with 30% isodose line overlapping the brainstem (**C**), and the use of 2 isocenters (**D**). Purple line indicates the brainstem area (for further DVH measurements); light blue line, the trigeminal nerve; green line, the 50% isodose line; and dark blue area, approximate middle point of trigeminal nerve, in the retrogasserian area. Figure is available in color online only.

ies agreeing that the maximum interval for pain relief can be considered 180 days after radiosurgical treatment.

Hypesthesia and/or Other Complications and Time Points

Hypesthesia onset (all BNI scores included, crude rates) among the studies was as follows (mean and median [range]): for GKS, 21.7% and 19% (0%–68.8%); for LINAC, 27.6% and 28.5% (11.4%–49.7%); and for CKR, 29.1% and 18.7% (11.8%–51.2%; Table 4). The difference in the onset of hypesthesia between GKS and LINAC studies was not statistically significant ($p = 0.22$, 2-sample t-test), with a difference of -5.89% between the means. However, the follow-up for LINAC studies was more limited in time; therefore, the incidence of hypesthesia was probably underestimated.

The difference in the onset of hypesthesia between GKS and CKR studies was not statistically significant ($p = 0.43$, 2-sample t-test), with a difference of -7.46% between the means. However, the follow-up period for the CKR studies was more limited in time, with an eventual underestimation of this reported outcome. Furthermore, the technical nuances of each technique preclude a fair comparison between the two.

The mean time to hypesthesia onset in the GKS group

ranged from 6 to 36 months, and the time varied from 1 to 94 months. Time to hypesthesia onset was not reported in the CKR and LINAC studies.

Bothersome or very bothersome hypesthesia onset (BNI scores III and IV) was reported as follows: for GKS studies, it ranged from 0% to 17.3%, with a mean of 3.1% and a median of 0%; for LINAC, one study reported 13.6%; and for CKR studies, it ranged from 5.9% to 12%, with a mean of 9.3% and a median of 10%. The difference between the GKS and CKR studies was statistically significant for BNI scores III and IV ($p = 0.05$, 2-sample t-test), with a difference of -6.19% between the means.

Data for complications other than hypesthesia are also presented in Table 4.

Recurrence Rates and Time Points

The mean and median recurrence rates for the GKS studies were 24.6% and 23%, respectively (range 0%–52.2%; Table 4). For LINAC-based studies, the mean and median rates were 32.2% and 29%, respectively (range 19%–63%). For CKR-based studies, the mean and median rates were 25.8% and 27.2%, respectively (range 15.8%–33%). The difference between the GKS and LINAC studies was statistically significant for BNI scores III and IV ($p =$

TABLE 3. Freedom from pain response and interval to the response

Authors & Year	FFP w/ Medication (%)	FFP w/o Medication (%)	Mean &/or Median TTPR (days)	TTPR Range (days)
GKS studies				
Régis et al., 1995	80.00	80.00	20.5*/25.5†	1–30
Kondziolka et al., 1996 ⁵⁹	86.00	—	—	—
Kondziolka et al., 1996 ⁶¹	94.00	58.00	30†	1–201
Young et al., 1997	88.20	74.50	—	1–120
Kondziolka et al., 1998	86.00	60.00	—	—
Kannan et al., 1999	66.60	100.00	—	30–90
Chang et al., 2000	100.00	46.70	18.8*	1–93
Rogers et al., 2000	96.00	35.00	15*	0–192
Maesawa et al., 2001	78.60	64.90	60†	0–61.2
Zheng et al., 2001	93.75	52.50	22*	1–120
Matsuda et al., 2002	100.00	60.60	17*	0–240
Pollock et al., 2002	75.00	59.00	21†	1–140
Petit et al., 2003	77.00	42.00	21†	0–168
Shaya et al., 2004	70.00	40.00	—	—
Massager et al., 2004	89.40	68.10	—	—
Cheuk et al., 2004	89.60	52.10	14†	0–168
Drzymala et al., 2005	81.10	52.70	—	—
McNatt et al., 2005	75.00	32.00	38.5*	—
Sheehan et al., 2005	70.00	44.00	24*	1–180
Tawk et al., 2005	71.00	44.00	—	—
Urgosik et al., 2005	96.00	80.40	90†	1–390
Régis et al., 2006	97.00	83.00	10†	0–175
Longhi et al., 2007	90.00	61.00	—	—
Little et al., 2008	83.00	41.00	—	—
Huang et al., 2008 ⁴⁷	77.50	56.00	33*	2–180
Dellaretti et al., 2008	98.70	—	78*	—
Azar et al., 2009	83.00	40.00	—	—
Han et al., 2009	90.20	51.70	—	—
Dhople et al., 2009	81.00	64.00	14†	14–84
Riesenburger et al., 2010	83.00	32.10	54*	1–180
Verheul et al., 2010	75.00	60.00	—	—
Kondziolka et al., 2010	89.00	28.60	30†	1–360
Park et al., 2011 ¹⁰⁰	—	—	—	—
Loescher et al., 2012	71.00	39.00	—	—
Hayashi et al., 2011	98.00	66.00	21†	—
Park & Hwang, 2011	100.00	—	28†	30–480
Lee et al., 2012	—	—	—	—
Marshall et al., 2012	86.00	43.00	—	1–90
Elaimy et al., 2012	71.00	31.00	—	—
Young et al., 2013	85.60	43.70	51.1†	4.9–81.9
Lee et al., 2013	97.80	—	—	—
Aykol et al., 2014	68.80	29.00	50.4*/60†	30–120
Karam et al., 2014	80.50	49.00	48*	1–180
Lucas et al., 2014	84.50	—	—	—
Régis et al., 2016 ¹¹⁴	91.75	—	10†	1–180
CKR studies				
Romanelli et al., 2003	70.00	40.00	—	—
Lim et al., 2005	70.00	40.00	—	—

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TABLE 3. Freedom from pain response and interval to the response

Authors & Year	FFP w/ Medication (%)	FFP w/o Medication (%)	Mean &/or Median TTPR (days)	TTPR Range (days)
CKR studies (continued)				
Villavicencio et al., 2007	67.00	67.00	—	—
Fariselli et al., 2009	94.00	—	—	—
Adler et al., 2009	96.00	72.00	—	—
Lazzara et al., 2013	88.00	—	—	—
Tang et al., 2011	—	68.70	—	—
Peddada et al., 2011	100.00	—	—	—
Soboleva et al., 2012	50.00	50.00	—	—
LINAC studies				
Goss et al., 2003	76.00	76.00	60†	—
Smith et al., 2003	87.80	56.10	—	—
Frighetto et al., 2004	95.40	68.10	81*	0–360
Kubicek et al., 2004	78.00	35.00	—	—
Chen et al., 2004	90.90	43.20	28†	—
Richards et al., 2005	75.00	57.00	30*	—
Pusztaszeri et al., 2007	100.00	35.00	—	—
Zahra et al., 2009	95.00	40.00	—	1–70
Chen et al., 2010	90.90	43.20	28*	—
Dos Santos et al., 2011	82.70	17.30	—	—
Smith et al., 2011	88.50	71.30	57.6*	0–180

— = not available; TTPR = time to pain relief.

* Mean value.

† Median value.

0.15, 2-sample t-test), with a difference of -7.52% between the means. In contrast, the difference between the GKS and CKR studies was not statistically significant for BNI scores III and IV ($p = 0.81$, 2-sample t-test), with a difference of -1.18% between the means.

The mean time to recurrence ranged from 6 to 48 months (crude interval 1–150.1 months) for GKS studies, ranged from 7.5 to 20.4 months (crude interval 3–47 months) for LINAC studies, and was 9 months (crude interval 1–43 months) in the only CKR study reporting such data.³¹

Maintaining Pain Relief

The maintenance of pain relief was very rarely observed in the CKR and LINAC studies, with only Smith et al.¹²⁵ reporting 60% with pain relief at 3 years. After this time point, the other CKR and LINAC studies did not give details concerning their patients.

For GKS, notable studies reported outcomes at 7 and 10 years, respectively. At 7 years, the following rates of maintained pain relief were reported: Little et al., 32%;⁷⁴ Dhople et al., 22%;²⁵ and Régis et al., 59.7%.¹¹⁴ At 10 years, Kondziolka et al.⁶³ and Régis et al.¹¹⁴ reported rates of 30% and 45.3%, respectively.

Discussion

Timing of RS From Symptom Onset

Only one study, by Mousavi et al.,⁹¹ retrospectively ana-

lyzed a series of 121 patients treated with GKS as their initial surgical procedure (level IV evidence), using a single 4-mm isocenter and a uniform dose of 80 Gy. These authors concluded that earlier GKS (within 3 years of pain onset) led to a shorter time to pain relief, a longer interval of pain relief off medication (BNI score I), and longer adequate pain control (BNI score I–IIIA).

Stereotactic RS yields a better initial FFP response if it is performed in the first 3 years after pain onset (level III evidence).

Possible Radioprotective Effects of Medication at the Time of RS

Flickinger et al.³³ investigated the possible radioprotective effects of anticonvulsant medications that could alter the response to RS. They retrospectively analyzed 200 patients who had been treated with a maximal RS dose of 80 Gy and a unique 4-mm collimator, had not undergone previous MVD, and had a follow-up of at least 6 months (median 24 months, range 6–153 months). These authors concluded that the use of carbamazepine or gabapentin at the time of GKS does not reduce the percentage of patients obtaining pain relief and developing complications (facial numbness or paresthesias).

Target (Isocenter) Location and Selection

General Considerations

The technical goal of RS is to place a 4-mm isocenter

TABLE 4. Summary of complications

Authors & Year	Hypesthesia Overall (Mean %)	Hypesthesia BNI Scores III + IV (%)	Mean Time to Hypesthesia Onset in Mos (range)	Other Complications (%)	Recurrence (%)	Mean Time to Recurrence (mos)	Range of Time to Recurrence (mos)
GKS studies							
Régis et al., 1995	0	0	—	0	20.00	10.00	—
Kondziolka et al., 1996 ⁵⁹	0	0	—	0	—	—	—
Kondziolka et al., 1996 ⁶¹	6.00	0	—	0	—	—	—
Young et al., 1997	0	0	—	0	7.80	—	—
Kondziolka et al., 1998	10.00	0	—	0	—	—	—
Kannan et al., 1999	—	0	—	0	0.00	—	—
Chang et al., 2000	13.30	0	8.5	0	13.30	8.80	8–9
Rogers et al., 2000	14.00	0	—	0	21.00	6.70	1–20
Maesawa et al., 2001	—	0	10.2	Deafferentation pain 0.40	13.60	15.40	2–58
Zheng et al., 2001	12.00	0	—	0	9.30	—	5–26
Matsuda et al., 2002	17.10	0	(9–24)	Dry eye 9.1	9.10	8.70	6–12
Pollock et al., 2002	37.00	0	8 (2–20)	Bothersome dysesthesia 12.00	16.00	8.00	2–30
Petit et al., 2003	7.30	3.10	—	0	29.00	8.50	1–48
Shaya et al., 2004	17.50	0	—	0	42.80	—	2–10
Massager et al., 2004	38.00	4.30	—	0	8.00	13.20	—
Cheuk et al., 2004	11.60	1.00	—	0	—	—	—
Drzymala et al., 2005	43.20	16.90	(12–15)	0	—	—	—
McNatt et al., 2005	20.00	9.00	—	Keratitis 7.00, dysesthesia 16.00	23.00	9.60	2–36
Sheehan et al., 2005	19.00	10.30	—	0	27.00	12.00	2–34
Tawk et al., 2005	37.00	0	—	Paresthesia 13.00	—	—	—
Urgosik et al., 2005	20.00	0	36 (3–94)	0	25.00	36.00	6–94
Régis et al., 2006	5.00	0	—	Paresthesia 5.00	34.00	6.00	1–15
Longhi et al., 2007	2.50	0	8.4	Paresthesia 6.25	18.00	14.20	—
Little et al., 2008	45.00	17.00	—	Dry eye 6.7	—	—	—
Huang et al., 2008 ⁴⁷	14.00	2.00	6 (1–36)	Keratitis 3.4	—	—	—
Dellaretti et al., 2008	21.00	10.50	—	0	26.30	—	6–42
Azar et al., 2009	13.00	0	—	0	—	—	—
Han et al., 2009	13.30	0	(2–52)	0	52.20	—	—
Dhople et al., 2009	—	6.00	—	0	—	—	—
Riesenburger et al., 2010	35.80	0	—	0	27.00	9.50	4–54
Verheul et al., 2010	29.00	6.00	—	Deafferentation pain 0.30	—	—	—
Kondziolka et al., 2010	10.50	3.20	—	Deafferentation pain 0.20	42.90	48.00	3–144
Park et al., 2011 ¹⁰⁰	21.00	0	—	Dry eye 1.6	—	—	—
Loescher et al., 2012	31.00	—	—	0	—	—	—
Hayashi et al., 2011	11.70	12.30	—	0	18.00	—	—
Park & Hwang, 2011	23.50	0	—	Dry eye 5.8	35.30	20.00	3–36
Lee et al., 2012	—	0	—	Dysesthesia 4.54	—	—	—
Marshall et al., 2012	52.00	0	—	Deafferentation pain 3.30, keratitis 2.7 (corneal anesthesia)	40.00	—	—
Elaimy et al., 2012	19.00	0	—	Paresthesia 7.00	—	—	—
Young et al., 2013	32.90	17.30	—	Dry eye 22.4	14.30	—	—

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TABLE 4. Summary of complications

Authors & Year	Hypesthesia Overall (Mean %)	Hypesthesia BNI Scores III + IV (%)	Mean Time to Hypesthesia Onset in Mos (range)	Other Complications (%)	Recurrence (%)	Mean Time to Recurrence (mos)	Range of Time to Recurrence (mos)
GKS studies (continued)							
Lee et al., 2013	37.40	13.20	—	0	15.40	32.00	10–62
Aykol et al., 2014	68.80	0	—	Dysesthesia 68.80	—	—	—
Karam et al., 2014	16.70	11.1 (IV)	—	0	41.40	—	—
Lucas et al., 2014	42.00	—	—	0	50.44	—	—
Régis et al., 2016 ¹¹⁴	21.10	2.20	12	0	34.40	24.00	0.6–150.1
CKR studies							
Romanelli et al., 2003	—	10.00	—	0	—	—	—
Lim et al., 2005	51.20	—	—	0	15.80	—	—
Villavicencio et al., 2007	47.00	12.00	—	0	31.00	—	—
Fariselli et al., 2009	—	—	—	0	33.00	9.00	1–43
Adler et al., 2009	17.00	—	—	0	—	—	—
Lazzara et al., 2013	11.80	5.90	—	0	23.50	—	—
Tang et al., 2011	18.75	—	—	0	—	—	—
Peddada et al., 2011	Oral mucositis	—	—	0	—	—	—
Soboleva et al., 2012	—	—	—	0	—	—	—
LINAC studies							
Goss et al., 2003	32.00	—	—	0	32.00	—	4–13
Smith et al., 2003	25.00	—	—	0	25.60	7.46	3–10
Frighetto et al., 2004	36.30	—	—	0	36.30	8.50	6–11
Kubicek et al., 2004	25.00	—	—	Dry eye 5.0	63.00	20.40	2–36
Chen et al., 2004	11.40	—	—	0	25.00	—	—
Richards et al., 2005	14.00	—	—	Keratitis 3.60	—	—	—
Pusztaszeri et al., 2007	—	—	—	0	29.00	—	4–13
Zahra et al., 2009	35.00	—	—	0	—	—	—
Chen et al., 2010	11.40	—	—	0	25.00	—	—
Dos Santos et al., 2011	36.00	—	—	0	34.60	20.00	4–47
Smith et al., 2011	49.70	13.60	—	Dry eye 19.5	19.00	13.50	—

— = not available.

(in GKS) or 5- or 7.5-mm collimator (in CKR or LINAC RS) on the trigeminal nerve as it courses the prepontine cistern. This technical choice is made since the nerve, surrounded by CSF at this level, is very well visualized using modern MRI techniques. These imaging techniques also allow for precise targeting and a very sharp dose fall-off (for example, penumbra) beyond the trigeminal nerve, reducing the risk of damage to the brainstem and/or temporal lobe.

Different Targets: From Leksell to Now

In a study published in 1991, Lindquist, who used the same target (gasserian ganglion) in all cases, evaluated and reported outcomes for 46 patients, 18% of whom had maintained pain relief at 2 years.³ In 1993, Rand et al. proposed moving the target to the cisternal segment of the trigeminal nerve, to what was called the “retrogasserian” or “far anterior cisternal” target (Fig. 2).^{109,115} Lindquist

subsequently promoted the elegant idea of targeting the REZ (also referred to as the “dorsal REZ” in the literature) where the nerve exits the brainstem with a lower dose of 70 Gy.³ Kondziolka et al.⁶³ and Régis et al.¹¹⁴ reported the results for FFP without medication at 10 years after targeting the REZ and the anterior cisternal target, respectively. These 2 studies are the only ones reporting such long-term follow-up.

Note, however, that anatomical placement of the target varies from 0 to 8 mm with regard to the nerve’s exit from the brainstem.

Rationale for Target Placement: A Histological Hypothesis

The major difference between the anterior and the posterior target probably relates to the dose received by the REZ and the brainstem and, more precisely, to the trigeminal nerve pathways within the brainstem. The REZ, also called the “Obersteiner-Redlich zone,” is histologically de-

defined as the place where peripheral myelination (Schwann cells) transitions to central myelination (oligodendrocytes). The REZ is not fixed, and its location can vary from 0 to 3 mm from the nerve's exit from the brainstem and is impossible to visualize on in vivo imaging. Some authors make the choice of an anterior versus a posterior target based on the idea that the nerve is more radiosensitive at the REZ than at the anterior part.

Target Placement and Related Complications: Indirect Evidence From Dose-Volume Histograms

Only 1 study documented dose-volume effects on the brainstem (dose-volume histogram [DVH]) in a comparison of 3 different devices: GK, LINAC, and CK.¹⁴² Xue et al.'s aim was to see whether complications after RS were correlated with dose distributions. These authors reviewed 32 cases that had been treated with GKS at their institution (Cooper University Hospital). All cases had utilized doses of either 80 or 85 Gy, had not been previously treated with surgery, and had a median follow-up of 25 months (range 4–39 months). The LINAC cases were obtained from the study of Gorgulho et al.,⁴⁰ and the CK cases were obtained from Lim et al.⁷² Xue et al. concluded that the most common complication was numbness.¹⁴² In the following cited GKS studies^{61,85,112,137,142} numbness was the only complication encountered, while other adverse events such as eye irritation and/or dryness,¹²⁵ neurotrophic keratopathy,¹¹⁶ anesthesia dolorosa, decreased corneal reflex, ipsilateral masticator weakness, trismus,⁷² and dysesthesias¹³⁸ appeared in the LINAC and CKR studies.

Brisman and Mooij¹⁵ evaluated radiosurgical efficacy in a series of patients, considering the association between the brainstem volume included in the 20% isodose line (VB20) and the volume of the trigeminal nerve that receives 50% or more of the maximum dose (VT50). These authors concluded that excellent results at 6 and 12 months positively correlated with VB20 values of 20 mm³ or more ($p = 0.018$). However, this study lacked long-term follow-up and, consequently, has limited analysis with regard to complication rates and their significant factors, as well as with regard to recurrence.

The worst complication reported with GKS was dry eye syndrome, in the study by Matsuda et al.,⁸⁹ who used the REZ target. While evaluating the DVHs, these authors determined that the maximal dose to the brainstem (cutoff > 25 Gy), as well as the position of the isocenter (cutoff < 4.5 mm) in relation to the exit of the trigeminal nerve from the brainstem, was statistically significantly related to complications. Additionally, a brainstem volume of more than 28 mm³ receiving more than 12 Gy of radiation was significantly related to complications (the only significant factor in the multivariate analysis).

Goss et al. conducted a study using LINAC RS and found a trend toward increased facial numbness when larger volumes of the brainstem were included in the 20% isodose line treatment plan.⁴² A similar (though not statistically significant) tendency was reported by Massager et al.,⁸⁵ who found that patients with facial numbness had received higher radiation doses to the brainstem than the patients with no facial numbness. That is, for the first 1 mm³ of the brainstem, a median dose of 12.85 Gy compared

with 10.6 Gy, respectively, had been administered. And for the first 10 mm³ of the brainstem, 10.6 Gy compared with 8.6 Gy had been delivered.

Cheuck et al. did not find any correlation between the appearance of facial numbness and the dose received by the brainstem.²¹ This is not surprising, however, as the doses delivered to the brainstem were rather low in their study, mostly ranging from 7 to 17.5 Gy (median 15 Gy), with 94.8% of the patients receiving a maximal dose ≤ 15 Gy ($p = 0.6832$). Moreover, the authors used plugging to limit doses to the brainstem. Neither was there a correlation between the FFP response and the dose administered to the brainstem.

Indirect evidence for target placement also comes from the study by Smith et al.,¹²⁵ who compared 3 different strategies with regard to the brainstem and maximal dose. The first group was treated with 70 Gy at the 30% isodose line, a second group received 90 Gy at the 30% isodose line, and a third group received 90 Gy at the 50% isodose line. The incidence of facial numbness increased from 35.7% to 48.9% to 59.3%, respectively.

In a study of 448 patients treated with a mean dose of 88 Gy (range 80–97 Gy) targeting the REZ, Marshall et al. found that the mean delivered dose in those who developed facial numbness (57.6 Gy) was higher than that in the patients without numbness (47.3 Gy; $p = 0.02$).⁸³

Régis et al.¹¹⁴ recently published a large series of 497 patients with more than 1 year of follow-up (median 4 years, range 1–14). The authors limited irradiation to 10 mm³ of the brainstem with a maximum dose of 15 Gy, using an anterior retrogasserian target. They reported 21% of patients with hypesthesia and 45.3% of patients with FFP without medication at 10 years.

Anterior Versus Posterior Target: Comparative and Retrospective Clinical Studies

Matsuda et al.⁸⁸ divided 100 patients treated with a single 4-mm isocenter into 2 different groups according to target—posterior target group, receiving 80 Gy at the proximal trigeminal nerve (REZ), and anterior target group (cisternal), receiving doses between 80 and 90 Gy at the retrogasserian portion of the trigeminal nerve. The median follow-up was 30 months (range 3–88 months). Initial and last follow-up pain relief were similar in the 2 groups (81.6% and 67.4% anterior compared with 92.2% and 68.6% posterior, respectively), as was the total percentage of complications (44.9% vs 37.3%, respectively). However, the authors found more bothersome complications in the anterior group (26.5% vs 11.8%), but there had been a significant increase in the prescribed dose (88.5 ± 3.6 vs 80 Gy) and the target had been very close to the plexus triangularis, as initially described by Leksell. Thus, the work of Matsuda et al. cannot be considered a true comparison between the anterior (as described by Régis et al.¹¹⁴) and posterior target.

Park et al.⁹⁹ retrospectively compared 2 different targeting methods of the retrogasserian versus the dorsal REZ. Thirty-nine cases were retrospectively reviewed after a mean follow-up of 26.1 months (range 12–53 months). Those with an anterior target had received a median dose of 85 Gy (mean 85.6 Gy, range 83–90 Gy) compared with

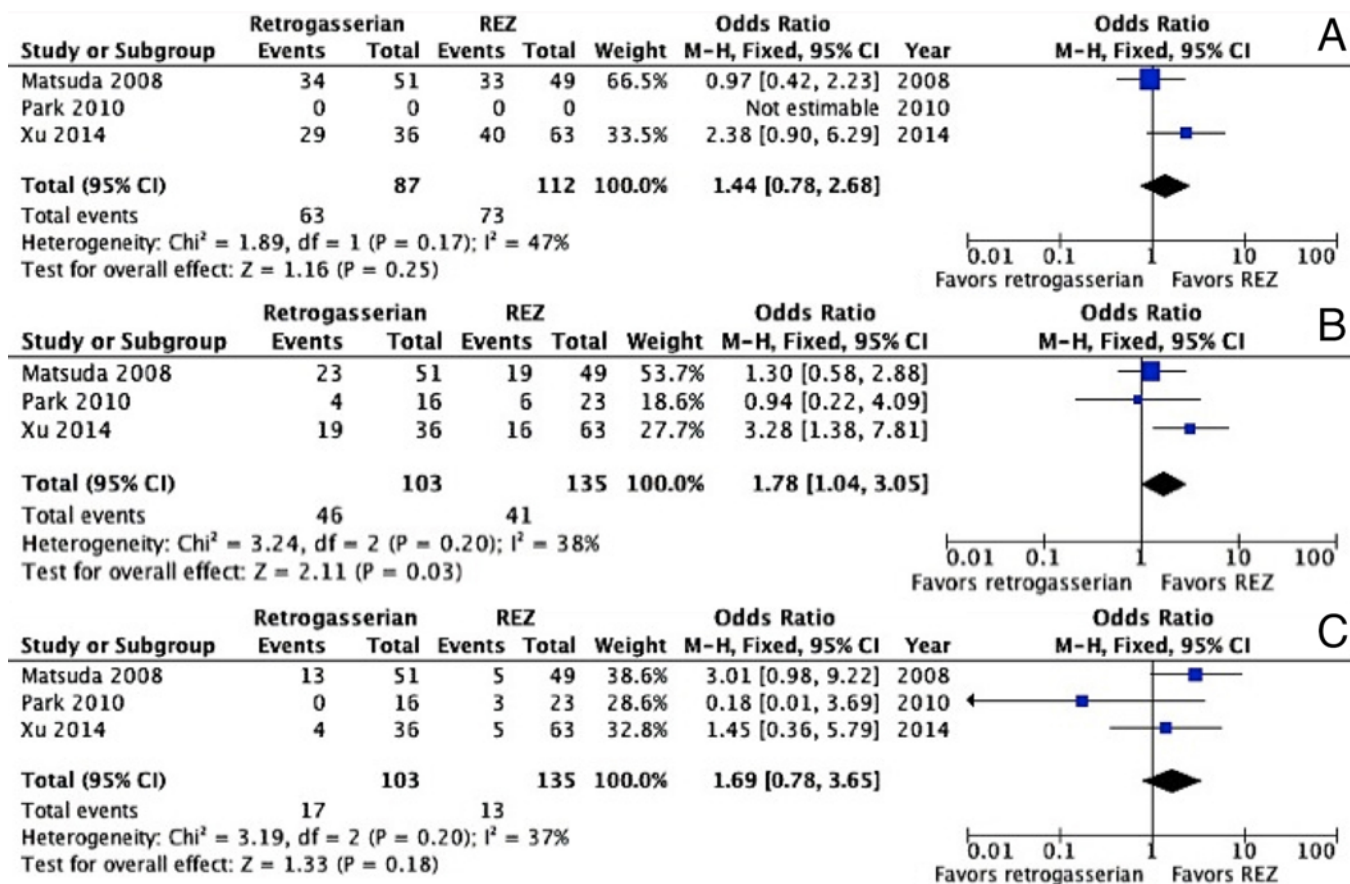


FIG. 3. When initial efficacy was pooled (A), there was no statistically significant difference between the retrogasserian and the REZ target, with an HR = 1.44 (95% CI 0.78, 2.68), $p = 0.25$. For toxicity (B), there was a statistically significant increase in the REZ group, with an HR = 1.78 (95% CI 1.04, 3.05), $p = 0.03$. For the maintenance of pain relief (C), there was no statistically significant difference between the two targets, with an HR = 1.69 (95% CI 0.78, 3.65), $p = 0.18$. Figure is available in color online only.

80 Gy (mean 82.6 Gy, range 80–90 Gy) in the posterior group. Initial pain relief was fairly comparable between the two groups, at 93.8% for the anterior group versus 87% for the posterior group. The time to a response to GKS was shorter in the anterior group, at a mean of 4.1 weeks compared with 6.4 weeks in the posterior group. While the total complication rate was similar in the two groups (25% anterior vs 26.1% posterior), bothersome facial numbness and dry eye syndrome were never encountered in the anterior group but did occur in the posterior group (13.1% and 8.7%, respectively). The authors concluded that for a similar range of doses, the anterior target had better outcomes with a similar rate of pain relief but with fewer bothersome complications.

Xu et al.¹⁴¹ retrospectively reviewed 99 cases treated with GKS at the same institution, targeting either the REZ (63 patients) or the retrogasserian portion (36 patients) with a maximum dose of 80 Gy. Kaplan-Meier analysis revealed that the durability of pain relief was only associated with the proximal location of the target ($p = 0.018$). Radiosurgery-induced facial numbness (BNI score II or III) was more frequent in the proximal REZ group than in the distal group (53% vs 25%, respectively, $p = 0.015$).

Figure 3 shows the results for comparisons of the ret-

rogasserian versus the REZ target. When initial efficacy was pooled, there was no statistically significant difference between the two targets, with an HR = 1.44 (95% CI 0.78, 2.68), $p = 0.25$ (Fig. 3A). For toxicity, there was a statistically significant increase in the REZ group, with an HR = 1.78 (95% CI 1.04, 3.05), $p = 0.03$ (Fig. 3B). For the maintenance of pain relief, there was no statistically significant difference between the two targets, with an HR = 1.69 (95% CI 0.78, 3.65), $p = 0.18$ (Fig. 3C; level II evidence).

Currently, given level II evidence, the ISRS favors an anterior target. This preference is mainly based on retrospective comparative studies, which have demonstrated that the anterior retrogasserian target has, in terms of FFP, an outcome similar to that with a posterior target but with a less bothersome hypesthesia complication, no development of other complications, and extended long-term pain relief. Furthermore, from the studies analyzing DVHs, there is evidence that increasing the dose to the REZ and/or the brainstem (VB20, VB50, and so forth) will increase the probability of numbness. The funnel plots including the comparative studies show a statistically significant effect in favor of the anterior target, with similar initial efficacy, less toxicity, and extended FFP on a long-term basis.

Anterior and posterior targets have similar initial effi-

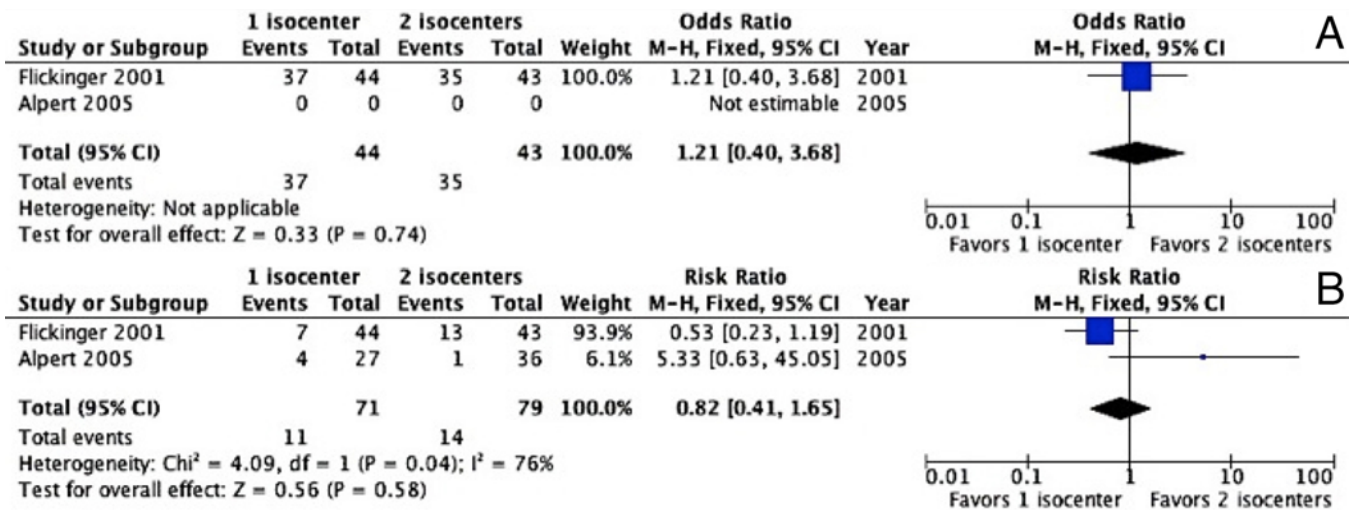


FIG. 4. When initial efficacy was pooled (A), there was no statistically significant difference between 1 and 2 isocenters, with an HR = 1.21 (95% CI 0.40, 3.68), $p = 0.74$. For toxicity (B), there was no statistically significant difference in the number of isocenters used, with an HR = 0.82 (95% CI 0.41, 1.65), $p = 0.58$; however, the study by Flickinger et al.³² clearly shows a major increase in toxicity with 2-isocenter use. Figure is available in color online only.

cacy (level II evidence). The anterior target has lower hypesthesia and bothersome hypesthesia rates than the posterior target (level II evidence). Additional complications, including dry eye syndrome, are seen only with the posterior target (level II and III evidence). The anterior target, as compared to the posterior one, may result in higher pain relief rates on a long-term basis (level II and III evidence).

Isocenters: Their Number and the Use of Concentric Ones One Versus Two Isocenters

Flickinger et al.³² organized a prospective, double-blind randomized study (the only current randomized trial on stereotactic RS for TN) including 87 patients treated with 75 Gy using either one (44 patients) or two (43 patients) 4-mm isocenters at a retrogasserian target. After a median follow-up of 26 months (range 1–36 months), though pain relief was similar in the two groups, the authors concluded that the use of 2 isocenters significantly increases complications, mainly hypesthesia (including the bothersome type), due to the increase in the volume of the treated nerve ($p = 0.018$).

The question on the number of isocenters to use was also addressed by Alpert et al.⁴ in a cohort of 63 patients undergoing GKS with either one (27 patients) or two (36 patients) 4-mm isocenters at the REZ, using doses of 70–95 Gy. These authors concluded that patients treated with two isocenters were more likely to receive a higher radiation dose (mean 88.3 vs 79.1 Gy, $p < 0.001$) and have a greater improvement score (mean 2.83 vs 1.72, $p = 0.003$). Hypesthesia appeared in 5 cases (1 in the two-isocenters group and 4 in the one-isocenter group, all mild cases). Median follow-up was 10 months (range 3–63 months).

Pollock et al.¹⁰⁶ described the length of nerve treated with one or two 4-mm isocenters, which (within the 50% isodose line) was a median of 5.9 mm (range 5.2–6.3 mm) in the first group (one isocenter) compared with 9.4 mm (range 7.4–11 mm) in the second (two isocenters). The au-

thors found no significant relationship between the length of irradiated nerve and post-RS complications.

Dos Santos et al.²⁶ documented 3 cases of brainstem edema while reporting outcomes for essential TN treated with LINAC RS. Interestingly, the authors had used 2 collimators in these cases and stated that the use of 2 rather than 1 collimator had increased the median dose to the brainstem (from 4.5 to 7.2 Gy, respectively). They subsequently abandoned the use of 2 collimators.

Figure 4 shows the results of comparisons in the number of isocenters used. When initial efficacy was pooled, there was no statistically significant difference between 1 and 2 isocenters, with an HR = 1.21 (95% CI 0.40, 3.68), $p = 0.74$ (Fig. 4A). For toxicity, there was no statistically significant difference in the number of isocenters used, with an HR = 0.82 (95% CI 0.41, 1.65), $p = 0.58$ (Fig. 4B); however, the study by Flickinger et al. clearly shows a major increase in toxicity with the use of 2 isocenters (the so-called Flickinger effect, level II evidence).³²

One 4-mm Isocenter Versus Concentric 4- and 8-mm Isocenters

The issue of one 4-mm isocenter compared with concentric 4- and 8-mm isocenters was addressed by Kanter et al.,⁵⁴ who retrospectively reviewed 101 cases treated with GKS using either a single 4-mm isocenter (54 patients) or combined 4- and 8-mm isocenters (47 patients). A maximal dose of 75 Gy was targeted at the retrogasserian part of the trigeminal nerve. The authors concluded that the use of combined concentric isocenters did not improve outcome in terms of efficacy but did significantly increase numbness (22.6% compared with 2.9% at 2 years, $p = 0.0002$; level II evidence).

A Longer Segment of Treated Nerve and the Integral Dose to the Nerve

In a bicentric comparative study,⁸⁶ Massager et al. analyzed a cohort of 358 patients (259 treated in Marseille and

109 treated in Brussels) who had undergone 3 different targeting strategies: 90 Gy and no beam channel blocking (Marseille only, group 1), 90 Gy and no blocking (Brussels and Marseille, group 2), and 90 Gy with blocking (Brussels only, group 3). The radiation dose delivered to the nerve root in these 3 groups was significantly associated with the incidence of mild (15%, 21%, and 49%, respectively) and bothersome (1.4%, 2.4%, and 10%, respectively) trigeminal dysfunction. The good pain relief rates were 81%, 85%, and 90%, respectively, and the excellent pain relief rates were 66%, 77%, and 84%, respectively. The authors concluded that the use of a similar target, the incidence of trigeminal dysfunction, and pain relief can vary according to the radiation energy received by the retrogasserian portion of the trigeminal nerve root (mean respective doses: 32.17, 38.01, and 42.86 Gy). The prescription dose and the use of channel blocking modify the integral dose to the nerve (2.18, 2.76, and 3.28 mJ, respectively).

In another study, Massager et al.⁸⁷ retrospectively analyzed 109 patients who had been treated with GKS using an anterior cisternal target and a dose of 90 Gy. In 49 patients, beam channel blocking was used to reduce the dose delivered to the brainstem; 60 cases were treated without blocking. The authors found that channel blocking was significantly associated with a longer length of nerve exposed to high-dose radiation and a higher mean dose (42.86 Gy vs 38.01 Gy, respectively, $p = 0.002$) to the trigeminal nerve. More patients with blocking achieved an excellent pain outcome (84% vs 62%) but had a higher incidence of moderate and bothersome hypesthesia (37% and 10% vs 30% and 2%, respectively). Therefore, the authors recommend avoiding beam channel blocking for a 90-Gy dose since this increases the length of the treated nerve and thus toxicity. Additionally, the integral doses within the nerve were 3.35 and 3.12 mJ, respectively ($p = 0.027$).

Villavicencio et al.¹³⁸ analyzed outcomes for patients who had undergone CKR and concluded that treating longer lengths of the nerve was associated with both better pain relief and a higher incidence of hypesthesia. In another CKR study, Lim et al.⁷¹ retrospectively analyzed 29 patients in whom a length between 6 and 8 mm of the cisternal portion of the trigeminal nerve was irradiated using a median dose of 66.4 Gy (range 60–70 Gy) based on CT cisternography. While initial pain relief was excellent (90%) with a short latency to pain relief (median 6 days), the complication rate was high. A moderate or severe increase in trigeminal dysfunction was found in 4 (14%) and 3 (10%) patients, respectively. A decrease in the corneal reflex was found in 6.9% of the cases. Anesthesia dolorosa was found in 6.9%, as was ipsilateral masticatory weakness, with 1 patient (3.45%) presenting with transient diplopia.

Do not increase the length of the treated nerve: use only one 4-mm isocenter. Using 2 isocenters (either continuously or concentrically) yields similar rates of initial efficacy but with increased toxicity (the so-called Flickinger effect). Do not use beam channel blocking at 90 Gy (level I and II evidence).

Dose Selection

The optimal maximal dose selection remains a matter of debate. The doses delivered with RS usually vary from

60 to 90 Gy. It is worth noting that target selection and dose prescription are not done in the same manner for all RS techniques. In general, while dose is prescribed “on one point” in GKS, there is instead a dose prescription for a certain volume in LINAC RS or CKR. Typically, pain relief is considered modest with doses less than 80–90 Gy, whereas an overdose (more than 90 Gy) can lead to similar rates of pain relief but more complications. Most articles consider a dose between 70 and 90 Gy for a primary treatment, but which dose is optimal on an individual basis is unknown.

Kondziolka et al.⁵⁹ was the first to address this issue in a study of 51 patients with typical TN, treated with a dose range between 60 and 90 Gy. The authors concluded that a maximum dose of 70 Gy, as compared with 60 Gy, was associated with a significantly greater chance of complete pain relief ($p = 0.04$). This conclusion has been confirmed by a multicentric study by the same group,⁶¹ which found dose to be the unique factor influencing the complete response rate (including initial and last follow-up) in a multivariate analysis ($p = 0.016$). Note, however, that the former study included multiple target strategies, heterogeneous criteria for patient inclusion, and so forth.

Shaya et al.¹²⁰ also evaluated dose as a predictive factor. Among a series of 40 patients, 4 were treated with 70 Gy, 32 with 80 Gy, and 4 with 90 Gy. The failure rate at the last follow-up was significantly associated with dose (70 Gy with 100% failure vs 80 or 90 Gy with 22.2% failure, $p = 0.04$).

Kim et al.⁵⁸ addressed the issue of dose within the framework of a retrospective study of an REZ target (situated 2–4 mm anterior to the entrance of the nerve into the brainstem) in a series of 104 patients treated with doses of 80 Gy (60 patients) and 85 Gy (44 patients). The authors concluded that the use of 85 Gy brought more rapid clinical improvement without causing more complications. The 3-year actuarial FFP rate was similar between the two dose groups, 61.2% compared with 60.3%.

Longhi et al.⁷⁷ evaluated dose in a retrospective study that included 160 patients treated with 1 isocenter at a distance 2–5 mm from the exit of the nerve, using a mean dose of 85 Gy (range 75–95 Gy). In a univariate ($p = 0.007$) and multivariate ($p = 0.0001$) analysis, a maximal dose greater than 80 Gy was significantly related to a BNI score I outcome and a pain-free outcome, respectively. Additionally, 70% of the encountered complications occurred in patients treated with a dose higher than 90 Gy. The authors concluded that even though a maximal dose > 90 Gy is linked to a more favorable outcome, it can also lead to a higher incidence of complications. We have therefore concluded that a maximal dose of 90 Gy is an appropriate upper limit.^{63,106,114,115,125}

Indirect evidence also comes from histological studies. Zhao et al.¹⁴⁸ irradiated the trigeminal nerve in 5 rhesus monkeys, with doses ranging from 60 to 100 Gy (60, 70, 80, or 100 Gy). They concluded that doses of 60 and 70 Gy have very little impact on the structure of the trigeminal nerve, whereas a dose of 80 Gy can cause partial degeneration with the loss of axons and demyelination. Importantly, doses of 100 Gy can cause some necrosis of neurons. The mechanism of pain relief is believed to be focal axonal de-

generation of the trigeminal nerve that affects pain fibers proportionally more than sensory fibers.^{60,128}

The minimal effective dose is 70 Gy (level II evidence). The maximal effective dose is 90 Gy (level III evidence). Beyond 90 Gy, the efficacy rate remains similar but with a higher complication rate (level III evidence).

Dose Rate Influence

The literature regarding the influence of the radiation dose rate on outcomes after treating classical TN with GKS comprises very few studies^{6,10} despite a large number of trials confirming the safety and efficacy of GKS as a first-line and/or second-line treatment.¹¹³ Balamucki et al.¹⁰ concluded that there is no observable effect of dose rate or treatment duration on the control of facial pain and that patients should be confident in receiving optimal care with GKS at any time during the first half-life of cobalt sources. Arai et al.⁹ recommended no adjustment in the maximum dose to the treated nerve in a TN procedure when the GK is operating within a radiation dose rate range of 1.21–3.74 Gy/min. More recently, Lee et al.⁶⁸ suggested that a higher dose rate may provide earlier and longer-lasting pain relief (dose rate > 2 Gy/min), along with a lower recurrence rate at a later follow-up. These findings were obtained in a study of 133 patients uniformly treated with a dose of 80 Gy, with a single 4-mm isocenter without blocking, and within a dose rate range from 1.28 to 2.95 Gy/min.

Single-Fraction Versus Hypofractionated RS

Fraio et al.³⁶ retrospectively evaluated 23 patients who had undergone single-fraction RS (40 Gy) versus 22 patients who had been treated with hypofractionated stereotactic radiotherapy (HSRT; total dose 72 Gy in 6 fractions), delivered to the retrogasserian cisternal portion of the trigeminal nerve. The mean follow-up was 3.9 years. A BNI score of I–IIIB was achieved in 95.6% of patients treated with single-fraction RS and 100% of those treated with HSRT. The recurrence rate was lower in the single-fraction group (8.7% vs 27.3%), whereas facial numbness appeared in 8.7% of cases in the single-fraction group and none in the other group. The authors concluded that single-fraction RS resulted in more effective pain control than HSRT.

Single-fraction RS is better than hypofractionated RS (level II evidence).

Targeting the Trigeminal Nerve Based Only on CT Images

Four studies addressed the issue of targeting the trigeminal nerve with CT, 3 GKS studies and 1 CKR study, each using either CT only or CT cisternography.^{7,71,96,140} The study by Park et al. included 21 patients who were treated with a median dose of 80 Gy and had a median follow-up of 35 months.⁹⁶ Treatment outcomes were compared with those in 459 patients who had undergone MRI-guided GKS for TN at the same institution. These authors concluded that the rate of pain relief was similar in the 2 patient groups. They additionally indicated that, for cases involving the use of a head frame, the posterior pins should be placed at least 1 cm away from theinion to reduce pin- and frame-related artifacts on the targeting CT.

In patients with medically refractory TN who are unsuitable for MRI, CT targeting remains an appropriate option. Computed tomography is likely to ensure that the treated population will not have a higher rate of toxicity and/or pain recurrence.

Factors Influencing Initial or Later Pain Relief and Associated Complications

General Aspects

Several variables have been associated with the initial FFP response. Positive predictors before RS are an increased age,^{83,121} age more than 70 years,^{43,57} and typical pain.⁷⁷ Negative predictors before RS include multiple sclerosis,^{13,62,76,90,112,137} prior surgery^{57,74,82,103,106,132} or ablative procedures,^{86,132} an atypical component,^{82,118} appearance or aggravation of a sensory deficit,⁸² previous MVD,^{66,75,120,133} age under 70 years,¹³² age under 60 years,¹¹² distance between the isocenter and the exit of the nerve > 8 mm,¹¹² and diabetes mellitus.⁸³ Later pain relief maintenance following RS has been positively associated with new facial numbness^{63,106,118,132} and no past surgery²⁵ and negatively associated with a better initial response.¹¹⁸

The factors associated with hypesthesia onset and/or other complications have already been described.

Particular Aspects

Neurovascular Conflict and Its Effect on Pain Relief. The presence of a neurovascular conflict was found either to have no significance or to induce a favorable response. Additionally, a positive therapeutic response has been correlated with a higher dose to the point of contact between the impinging vessel and the nerve. Brisman et al.¹⁴ studied 179 patients treated using RS, with 59% presenting with a neurovascular conflict. These authors concluded that in cases without previous surgical treatment and with neurovascular conflict, the response to GKS was particularly favorable (BNI score I in 60% vs 31% with pain relief at the last follow-up, $p = 0.009$). Erbay et al.³⁰ analyzed 40 patients, 30 (75%) of whom had a preoperative neurovascular conflict. Twenty-five (83.3%) of the 30 patients had an adequate short-term response to GKS. The patients with a neurovascular conflict were 7 times more likely to have an adequate response to GKS than the patients without a neurovascular contact (OR 7.5).

In contrast, in the study by Shaya et al.,¹²⁰ 14 (35%) of 40 patients had a neurovascular conflict, and its presence did not significantly affect outcome ($p = 0.6$). Massager et al.⁸⁵ found no statistically significant relationship between the 3 subcategories of pain relief studied and the appearance of a neurovascular conflict on MRI. Sheehan et al.¹²² retrospectively analyzed 106 cases treated with GKS as a first-line treatment, using the REZ as a target and a mean maximal dose of 78.7 Gy (range 70–90 Gy). The median follow-up was 31 months. Sixty-three cases (59%) had a neurovascular conflict. The authors concluded that there was no significant difference in pain relief between those with and those without vascular impingement after GKS ($p > 0.05$). Additionally, pain relief correlated with a higher dose to the point of contact between the impinging vessel and the nerve.

A neurovascular conflict is not a negative predictor for RS (level II evidence).

Major Neurovascular Conflict by the Megadolichobasilar Artery and Its Effect on Pain Relief. Three studies addressed the issue of megadolichobasilar artery compression and its effect on the relief of pain.^{97,127,135} While Soma-za et al.¹²⁷ presented only a case report (2 shots of 4 and 8 mm, gasserian ganglion target), the other 2 studies included 20⁹⁷ and 29¹³⁵ cases. The initial pain relief rate (BNI score I–IIIB) was high and varied between 75% and 100%, with a low complication rate between 0% and 13%. The recurrence rate ranged between 0% and 24.1%. At 5 years, the FFP rate varied between 10% and 75.7%. In their study, Park et al.⁹⁷ concluded that there was no significant difference between patients with vertebrobasilar ectasia (VBE) and those without in terms of the rates of initial complete pain relief ($p = 0.6$), time to pain recurrence ($p = 0.25$), and postoperative sensory changes ($p = 0.73$); however, long-term results at 5 years were better in the patients without VBE (42% vs 10%). In the series by Tuleasca et al.,¹³⁵ both initial pain relief and long-term pain control were better than in their general series,¹¹⁴ with a low complication rate. In selected cases, RS can be a safe and valuable alternative for this particular anatomical condition.

Focal Enhancement of the Fifth Cranial Nerve and/or Brainstem After RS. Alberico et al.² studied the issue of focal enhancement of cranial nerve V after GKS in a cohort of 15 patients who had received doses ranging between 70 and 90 Gy and had undergone MRI within 5 months after the procedure. In 10 cases (66.7%), radiosurgical target site enhancement was seen. All 5 patients with an unchanged trigeminal nerve radiological aspect had been treated with 70 Gy ($p = 0.06$). No correlation between enhancement and treatment response or time to follow-up was seen ($p > 0.05$). Enhancement was seen as early as 32 days and as late as 188 days after treatment.

Friedman et al.³⁸ evaluated radiological responses for 26 patients who had been treated with doses ranging between 70 and 90 Gy targeting either the REZ (21 patients) or the retrogasserian portion of the nerve (5 patients). Magnetic resonance imaging was performed at 3–6 months after RS in 21 patients. In 19 of these patients (90.5%), no changes were identified in the trigeminal nerve or adjacent brainstem. The onset of a therapeutic effect ranged from 3 weeks to 3 months. In 2 cases with multiple sclerosis, abnormal signal and enhancement of the brainstem and/or trigeminal nerve was seen, without any clinical complications. The authors concluded that the results of enhanced MRI 3–6 months after RS do not correlate with clinical response.

Massager et al. studied a group of 78 patients treated with GKS for TN, 65 of whom had a 6-month MRI follow-up, which showed focal contrast enhancement of the trigeminal nerve.⁸⁴ The authors coregistered the follow-up MRI studies with the radiosurgical planning MRI studies. Target accuracy was assessed from deviation of the coordinates of the intended target compared with the center of enhancement on postoperative MRI. The radiation dose delivered at the borders of contrast enhancement was also evaluated. The authors concluded that the median deviation in clinical assessment of GKS for TN was low and compatible with its high rate of efficiency. Furthermore,

focal enhancement of the trigeminal nerve after RS occurred in 83% of their cases and was not associated with clinical outcome. Focal enhancement borders along the nerve root fit a median dose of 77 ± 8.7 Gy.

Gorgulho et al.⁴⁰ showed that gadolinium enhancement of the brainstem at the REZ has a significant correlation with both pain relief and numbness ($p = 0.008$ and 0.02 , respectively) and that trigeminal nerve enhancement does not correlate with outcome. Better pain relief and a higher incidence of numbness are correlated to a higher radiation dose delivered to the REZ at the brainstem.

Impact of a Previous Surgical Procedure. Previous Versus No Previous Surgery: Retrospective Comparative Studies. Fountas et al.³⁴ compared 2 groups, one without (52 patients) and one with (25 patients) previous surgeries. The 77-patient cohort was followed up over a period of 5 years and was treated with GKS using a median of 1 collimator (range 1–2 collimators), the REZ as the target, and a maximal median dose of 80 Gy (range 80–85 Gy), with the 30% isodose line adjacent to the REZ. In the group with no previous surgery, the initial response rate was 92.4% compared with 84% in the other group ($p = 0.16$). The excellent outcome rates (FFP without medication) at 1, 2, and 3 years after treatment were 80.8%, 69.2%, and 53.8% compared with 64%, 44%, and 12%, respectively ($p = 0.05$ at 2 years, $p = 0.01$ at 3 years). The authors concluded that a previous surgical procedure is a negative predictor for long-term pain control after GKS treatment. The hypesthesia rates were similar, 17.3% in the group with no previous surgery and 16% in the other group ($p = 0.48$). Two patients (8%) in the group with previous surgery developed bothersome facial tingling.

The same authors conducted a study published the following year,³⁵ which included 106 patients. They compared 2 groups without (57 patients) and with (49 patients) previous surgeries. The mean follow-up period was 34.3 months (range 12–72 months), and they used a median of 1 collimator (range 1–3 collimators), the REZ as the target, and a median maximal dose of 80 Gy (range 70–85 Gy). The initial response rate in those without previous surgery was 92.9% compared with 85.7% in the other group ($p = 0.13$). At 1 year after treatment, the FFP rates were 82.5% of those without previous surgery compared with 69.4% of those with, and the FFP rates were 78% and 63.5%, respectively, at 2 years after treatment ($p = 0.27$ and 0.39 , respectively). The hypesthesia rate was similar, at 15.8% of patients without previous surgery and 16.3% of those with such surgery ($p = 0.73$). Four cases (2 in each group) developed facial tingling and numbness.

Although not a comparative study itself, Dhople et al.²⁵ retrospectively analyzed 102 cases, which were separated into 2 groups according to a history of previous surgery or no such history. The difference in terms of actuarial pain relief at 1, 2, 3, 4, 5, 6, and 7 years, respectively, was as follows: 61%, 35%, 20%, 15%, 15%, 7%, and 7% of those with a history of previous surgery compared with 81%, 53%, 50%, 41%, 30%, 23%, and 23% of those with no such history.

Previous surgery is a negative predictor for pain relief after RS; this factor does not, however, contraindicate RS (level II evidence).

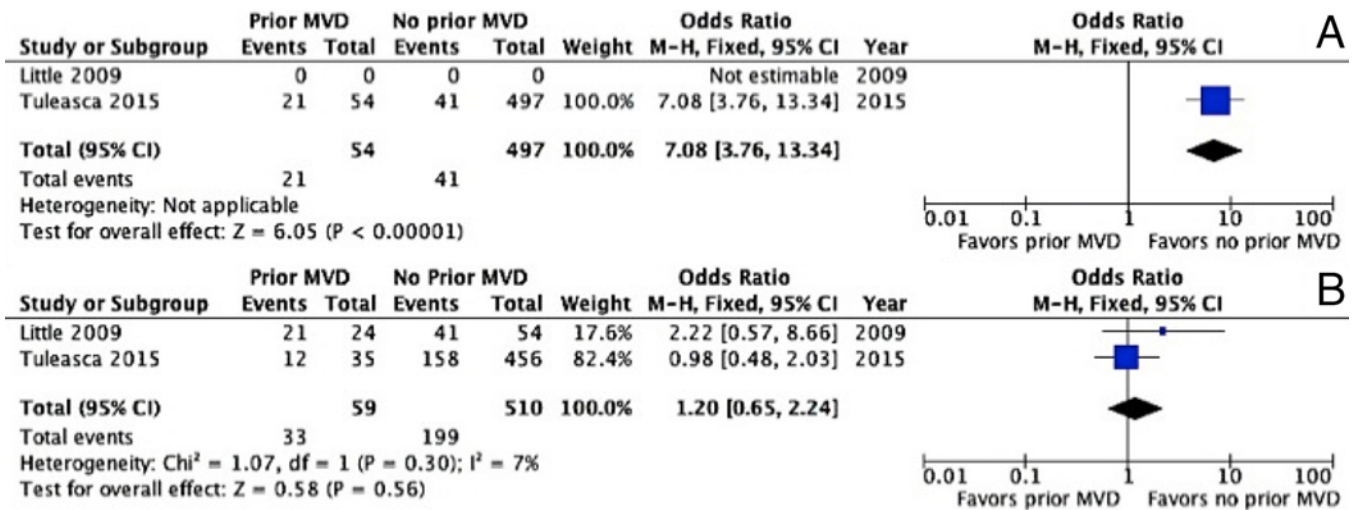


FIG. 5. When initial efficacy was pooled (A), there was a statistically significant difference between cases with prior MVD and those without, with an HR = 7.08 (95% CI 3.76, 13.34), p < 0.00001. For the maintenance of pain relief on a long-term basis (B), there was no statistically significant difference, with an HR = 1.20 (95% CI 0.65, 2.24), p = 0.56. Figure is available in color online only.

GKS After Previous Surgery: Retrospective Noncomparative Studies. Three other studies^{47,55,75} addressed the issue of GKS treatment as salvage therapy following a failed initial surgical procedure. Little et al.⁷⁵ retrospectively evaluated 79 patients who had received a median dose of 80 Gy (range 70–90 Gy) and had a median follow-up of 5.3 years. The initial FFP response was 91%, which is comparable to rates in general series. The actuarial pain relief rate at 5 years was 50%, with FFP in 20% of patients. Seven patients (10%) reported the development of facial numbness, and 8% described it as “very bothersome.”

Huang et al.⁴⁷ retrospectively evaluated 65 patients who had been treated with doses ranging between 70 and 90 Gy, a REZ target, and a unique 4-mm shot. The median follow-up was 64 months (range 18–32 months). The authors compared 3 different treatment groups: initial MVD and further GKS, initial GKS and further GKS, and initial percutaneous RFT and further GKS. There was no significant difference in terms of FFP: 74% versus 59% and 50%, respectively (p = 0.342). The overall recurrence rate was 35.4%, and recurrence appeared after a median time of 7 months (range 3–48 months). There was no significant difference in new facial numbness among the 3 treatment groups (p = 0.24). The FFP actuarial rates at 1, 2, and 3 years after treatment were 74%, 71%, and 66% of the patients, respectively.

Kano et al.⁵⁵ retrospectively reviewed 193 patients with TN treated with GKS after one or more previously failed surgeries. The median dose was 80 Gy (range 60–90 Gy), and the maximum follow-up was 14 years. After GKS, 85% of the patients achieved pain relief or improvement (BNI score I–IIIB). Pain recurrence was observed in 43.5% of the cases after a median of 72 months (range 6–144 months). Eighteen cases (9.3%) developed facial numbness (new or increased) and 1 case (0.5%) developed deafferentation pain.

GKS After Previous MVD. Two retrospective studies address the issue of GKS following MVD.^{75,133} Little et

al.⁷⁵ made an analysis of a subgroup of 24 patients treated with GKS after a previous MVD. The authors stated that at 5 years, only 12% of patients with prior MVD had FFP compared with 25% who had no history of MVD (p = 0.029). Tuleasca et al.¹³³ compared 54 prior-MVD cases with a cohort of 497 cases with more than 1 year of follow-up (range 14.1–144.6 months). The patients were treated at a retrogasserian target with a median dose of 85 Gy (range 70–90 Gy). Although not a case-control study, the authors found that patients with previous MVD had a significantly lower probability of initial pain cessation (77.8% vs 91.75%, p = 0.01). However, the probability of maintaining pain relief without medication was 44.3% at 10 years, similar to the rate in the larger cohort (45.3%, p = 0.85). Toxicity was low, with an actuarial hypesthesia rate of only 9.1% in the patients with prior MVD (BNI score II).

Figure 5 shows a comparison of cases with versus those without prior MVD. When initial efficacy was pooled, there was a statistically significant difference between the two, with an HR = 7.08 (95% CI 3.76, 13.34), p < 0.00001 (Fig. 5A). For the maintenance of pain relief on a long-term basis, there was no statistically significant difference between the cases with and those without prior MVD, with an HR = 1.20 (95% CI 0.65, 2.24), p = 0.56 (Fig. 5B)

Particular Follow-Up Aspects: The Risk of Vascular Damage After RS. Lorenzoni et al.⁷⁸ prospectively evaluated the maximal dose received by the SCA. In 55 patients treated with GKS for classical TN, who received a dose of 15 Gy or more to the SCA, and who had a minimum follow-up of 1 year, the study end points were SCA occlusion, stenosis, or infarction in the supplied territory. Fifteen patients whose SCA had received a mean maximal dose of 57.5 Gy (range 15–87 Gy) were ultimately analyzed. Neither obstruction nor infarction was demonstrated. In 1 patient, asymptomatic SCA stenosis, which was visualized distant to the irradiation field, was suspected. The authors concluded that the SCA could receive a high dose of radi-

tion during radiosurgical treatment, with no confirmation of any vascular damage induced by RS.

Yatshushiro et al.¹⁴³ reported a case of SCA occlusion with cerebellar infarction 15 months after GKS in a 55-year-old patient, with a dose between 65 and 75 Gy received by the artery.

Other cases that are not related to targeting of the trigeminal nerve in classical TN are not discussed here.

Quality of Life and Patient Satisfaction. Petit et al.¹⁰³ reported a median of 80% improvement in QOL after GKS, as a direct result of pain relief, and 65% of the patients believed that GKS was successful in their case. Patients in whom pain relief was maintained at the time of analysis reported a median 100% improvement in their QOL, with a 100% success rate. Those with temporary treatment responses (pain recurrence after a median of 8.5 months) described a median of 80% improvement in QOL with an associated 60% rate of treatment success. Jawahar et al.⁵¹ showed that patients' self-reported QOL scores improved 90% and that overall patient satisfaction was 80%. Régis et al. studied QOL for 100 patients treated with GKS and followed up prospectively.¹¹² The authors concluded that all QOL parameters were improved after RS ($p < 0.001$).

Azar et al.⁹ compared QOL before and after GKS, stating that statistically significant positive changes were encountered in all domains, except in physical function and in role limitation due to a physical problem. Pan et al.⁹⁵ evaluated QOL in 52 patients who were severely ill (BNI score IV or V) at baseline and were subsequently treated with GKS. The mean physical function score was 55.9 ± 7.7 before GKS and improved to a mean of 66.3 ± 8.1 at 3 months after GKS. The mean score for role limitation due to an emotional problem changed from 4.8 ± 9.9 at the time of GKS to 86.5 ± 12.6 at 3 months after GKS. The mean social functioning score changed from 32.0 ± 5.7 to 80.3 ± 8.7 .

In the series by Régis et al.,¹¹⁵ 93.1% of the patients had no regrets and said they would undergo RS again without hesitation, whereas 4.6% regretted having undergone the procedure and would not undergo it again.

Cost-Effectiveness Analysis

The cost-effectiveness analysis of TN surgery in general has been addressed in 5 studies.^{37,46,105,123,131} Pollock et al.¹⁰⁵ included 126 patients who underwent 153 interventions (33 MVD, 51 glycerol injection [GLR], 69 RS) and had a mean follow-up of 20.6 months. A higher percentage of patients who underwent MVD obtained and maintained excellent outcomes, compared with the patients who underwent GLR and RS (78% vs 55% and 52%, respectively, at 2 years; $p = 0.01$ for both). The authors concluded that the use of percutaneous procedures in older patients is supported by the results. Additionally, if the risk of general anesthesia is acceptable, MVD should be the preferred operation.

Tarricone et al.¹³¹ evaluated 20 patients undergoing CKR and 20 undergoing MVD, both groups including only patients with a BNI score of IV or V at baseline. The 2 procedures were equally effective at 6 months' follow-up but had different resources consumption: CKR reduced hospital costs by an average of 34% per patient. The au-

thors concluded that CKR is the cost-saving alternative to MVD.

Fransen³⁷ compared MVD to RFT, BMC, and GKS. This author concluded that percutaneous techniques are more cost-effective than GKS.

Sivakanthan et al.¹²³ evaluated the use and cost-effectiveness of 3 different surgical procedures by using the Medicare Claims database. A total number of 1582 claims were collected. In patients undergoing surgery, 51.1% underwent MVD, 41.5% RS, and 7.4% RFT. These authors concluded that the most frequently used surgical treatment was MVD, followed closely by stereotactic RS, and that RFT, despite being the most cost-effective, is the least used treatment modality.

Holland et al.⁴⁶ retrospectively analyzed a cohort of 89 patients who had undergone MVD (27 patients), RFT (23 patients), and RS (39 patients). At baseline, the patients significantly differed by age (mean 53.9 years vs 76.2 and 74.5 years, $p < 0.001$, MVD vs RFT and RS groups). Facial numbness significantly differed between the groups: 11%, 52%, and 28%, respectively ($p < 0.01$). At 2 years, the rates of recurrence requiring a new procedure were 22% compared with 74% and 31% ($p < 0.01$) in a mean time of 26 ± 29 , 59 ± 76 , and 35 ± 25 months, respectively. The authors concluded that MVD was the most expensive procedure, was performed in younger patients, and had the lowest rate of facial numbness and recurrence. Radiosurgery was slightly less costly, was more likely to be performed in older patients, and had a short-term recurrence rate similar to that for MVD. Radiofrequency rhizotomy was the least expensive with immediate pain relief but the highest rates of facial numbness and recurrence.

MVD Versus RS: Comparative Studies

The only prospective, nonrandomized cohort trial comparing MVD and GKS (dose 80–90 Gy, target REZ, brainstem receiving a maximum of 16 Gy at the 20% isodose line) was performed by Linskey et al.,⁷³ with outcomes reported for 80 patients (36 treated with MVD, 44 with GKS). Over a mean follow-up of 3.4 ± 2.14 years (range 0.17–8.5 years), the initial and last follow-up FFP rates were 100% and 80.6% for the MVD group and 77.3% and 45.5% for the GKS group, respectively. The respective actuarial FFP rates initially and at 2 and 5 years' follow-up were 100%, 88%, and 80% for the MVD group compared with 78%, 50%, and 33% for the GKS group ($p = 0.0002$). The permanent mild and severe sensory loss rates were 5.6% and 0% in the MVD group compared with 6.8% and 2.3% in the GKS group. Complications such as CSF leakage, hearing loss, and persistent diplopia (1 case each) were found only in the MVD group. The authors concluded that MVD should be preferred as the first-line surgical therapy in young and healthy patients, whereas GKS should be performed in those who are older, have significant medical problems, or refuse the recommended intervention of MVD.

In the framework of a retrospective study, Pollock compared patients (age < 70 years) who had undergone posterior fossa exploration (PFE; 55 patients) with those who had undergone GKS (28 patients).¹⁰⁴ At a mean follow-up of 25.5 months, PFE cases more commonly had FFP

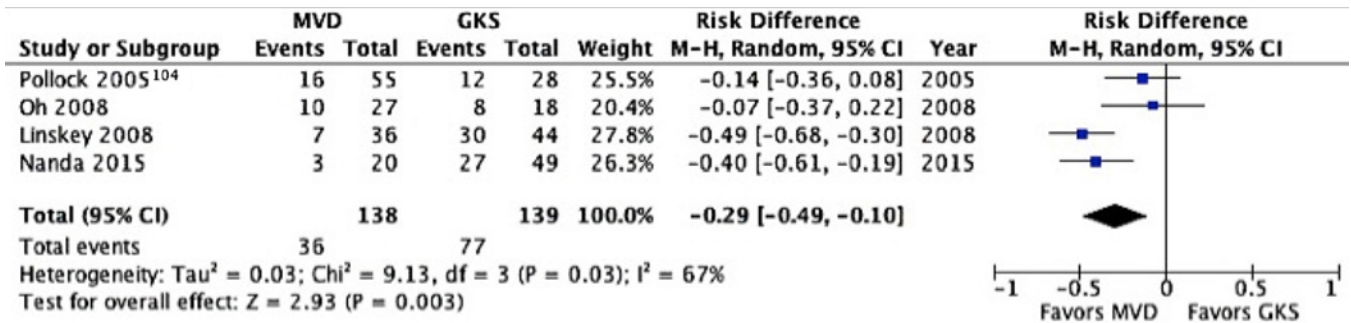


FIG. 6. When the maintenance of pain relief on a long-term basis was compared between MVD and GKS, there was a statistically significant difference, with an HR = -0.29 (95% CI -0.49, -0.10), p = 0.003. Figure is available in color online only.

without medication (75% at 1 year and 72% at 3 years vs 59% at both 1 and 3 years, p = 0.01). New facial numbness or dysesthesias appeared in 15% of the patients after PPE compared with 43% after GKS (REZ target and mean maximum dose of 89.1 Gy, p = 0.02).

Oh et al.⁹⁴ retrospectively evaluated older patients (age > 65 years) treated with MVD (27 patients) versus GKS (18 patients, target REZ, mean dose 77.8 Gy [range 70–84.3 Gy], one 4-mm collimator). At a mean follow-up of 35.9 months for the MVD group and 33.1 months for the GKS group, according to the BNI pain intensity scale, a better prognosis (63% vs 55.6% with score I or II) and an earlier response was found in the MVD group, with an identical recurrence rate in the 2 groups. Lower complication rates were seen in the GKS group, with only 1 case of dysesthesia (5.6%) compared with 2 cases of facial numbness and 1 case each of herpes zoster, CSF leakage, hearing disturbance, and subdural hematoma in the MVD group.

Nanda et al.⁹² retrospectively reviewed 20 patients treat-

ed with MVD and 49 treated with GKS, with no prior or further intervention and a median follow-up of 5.3 years. The authors concluded that there was no significant difference in terms of initial pain relief (100% MVD and 84% GKS, p = 0.055) or in recurrence (20% MVD and 39% GKS, p = 0.133). At the last follow-up, 85% of MVD cases had a BNI score of I compared with 45% of the GKS cases (p = 0.002). Patient satisfaction was the same in the 2 groups. However, this study lacks details about the technical nuances regarding GKS.

Figure 6 shows results of a comparison of MVD versus GKS. For the maintenance of pain relief on a long-term basis, there was a statistically significant difference, with an HR = -0.29 (95% CI -0.49, -0.10), p = 0.003.

However, the results previously described should be balanced with several factors, including the overall risk of complications. Microvascular decompression yields more risks than RS, including severe facial numbness (1.8%) or major complications such as chemical meningitis (19%), cerebrospinal fluid leakage (1.7%), ipsilateral hearing loss

TABLE 5. Final recommendations

Evidence Level	Recommendation
II	Single-fraction RS is better than hypofractionated RS
II	Previous surgery is a negative predictor for pain relief after RS; this factor does not, however, contraindicate RS
II	A neurovascular conflict is not a negative predictor for RS
II	The minimal effective dose is 70 Gy
I & II	Do not increase the length of the treated nerve: use only one 4-mm isocenter; using 2 isocenters (either continuously or concentrically) yields similar rates of initial efficacy but w/ increased toxicity (so-called Flickinger effect); do not use beam channel blocking at 90 Gy
II	An anterior target & a posterior target have similar initial efficacy
II	An anterior target has lower hypesthesia & bothersome hypesthesia rates than the posterior target
II & III	Additional complications, including dry eye syndrome, are seen only w/ a posterior target
II & III	An anterior target, as compared to the posterior one, has higher pain relief rates on a long-term basis (7 & 10 yrs' FU)
III	SRS is recommended as an alternative to the reference technique, which is MVD for classical trigeminal neuralgia
III	SRS yields a better initial freedom from pain response if performed in the first 3 years after pain onset
III	The maximal effective dose is 90 Gy
III	Beyond 90 Gy, the efficacy rate remains similar but w/ a higher complication rate
III	LINAC & CKR result in higher bothersome hypesthesia rates

Anterior target = placement of a unique 4-mm shot on the cisternal portion of the trigeminal nerve, at approximately 7–8 mm from its emergence from the brainstem; FU = follow-up; posterior target = placement of a unique 4-mm shot at the emergence of the nerve.

(1.3%), extraocular muscle palsy (1.2%), facial palsy (1%), and a very low postoperative death rate (0.2%).¹¹

Microvascular decompression is the reference technique, whereas SRS can be recommended as an alternative (level III evidence).

Percutaneous Procedures

Percutaneous techniques are ablative as they act by causing destruction of the nerve fibers via thermal energy (RFT), chemical damage (glycerol rhizotomy), or mechanical damage (BMC). Within this framework, they frequently cause facial numbness of variable grades as a condition of complete and sustained efficacy. Initial pain relief rates range between 90% and 97.6% for all of these techniques, and at 3 years the pain relief rate falls to between 53% and 69%, with severe numbness occurring in up to 20%–23% of patients. These procedures are notable for high recurrence rates (as high as 26% at a very short mean time of 18 months).^{16,20,56,93} Additionally, other procedure-related complications include exposure keratitis (0%–2%), anesthesia dolorosa (0%–2.5%), troublesome dysesthesias (4%–10%), and masticatory weakness (0–12%).^{16,20,56,93}

Quality of Reporting

Since 2003, Zakrzewska et al. have proposed a protocol for collecting data and reporting on surgical treatment for TN.^{22,147} The only RS paper that completely (with the exception of the follow-up period) fulfills such a practice remains the one written by Régis et al.¹¹² We believe that in future papers, for easier and more standardized comparison of the results, one should follow such recommendations.

Conclusions

Radiosurgery for TN is currently considered a minimally invasive alternative to the standard MVD. Technical refinements over time have aimed at improving the safety and efficacy of RS. The availability of MRI at the beginning of the 1990s largely contributed to the appraisal of this indication due to the direct and better visualization of the trigeminal nerve. Upfront radiosurgical treatment should be performed in cases with pharmacoresistance during the first 3 years after diagnosis. Although RS has lower pain relief rates on a long-term basis, careful and individual analysis should be made and the risks of both interventions should be balanced with a patient's age, anatomical condition, and potential benefit. While most analyzed series use the posterior target, comparative studies have demonstrated that the anterior retrogasserian target yields similar initial pain relief rates with a lower probability of toxicity (as well as a lower probability of bothersome and very bothersome hypesthesia) and higher maintenance of the FFP response on a long-term basis.

Although there is only one level I study (Flickinger et al.³²) and the rest of the studies comprise level II evidence, to help guide the management of patients with classical TN and given the limitations of the retrospective series, a number of consensus statements have been made (Table 5).

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Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods of care reasonably directed to obtain similar results. Physicians must make the ultimate judgment on the basis of the characteristics and circumstances of each individual patient. Adherence to these guidelines will not ensure successful treatment in every situation. The authors of these guidelines and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusions, or recommendations contained in this report.

Disclosures

Mr. Paddick has been a consultant for Elekta AB. Dr. Régis has been a consultant for Medtronic and has received support from Elekta for non-study-related clinical or research effort. Dr. Sahgal has received honoraria for past educational seminars from Medtronic, Elekta AB, Accuray Inc., and Varian Medical Systems and research grants from Elekta AB and belongs to the Elekta MR LINAC Research Consortium.

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