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REVIEW

The emerging role of gamma knife radiosurgery in the management of glossopharyngeal neuralgia

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Abstract Glossopharyngeal neuralgia (GPN) represents a rare craniofacial disorder accounting for about 1% of all craniofacial pain syndromes. GPN shares several pathophysiologic and clinical features with the more common trigeminal neuralgia. Medical therapy and microvascular decompression, in case of vascular nerve compression, represented the mainstay of GPN management. Other ablative therapies have been reported to date; however, few data are available because of the rarity of this pain syndrome. Among the ablative procedures, gamma knife radiosurgery (GKRS) has been recently introduced in the management of GPN with good pain control and low complication rates. Authors performed a systematic review of the published literature about GKRS in the management of GPN. Radiosurgical treatment data, pain control and recurrence rate have been analysed and compared. GKRS represented a valuable and effective treatment option for the management of GPN. Pain control and complication rates are better than those reported by other ablative procedures and microvascular decompression; however, future studies should be focused on the long-term efficacy of GKRS.

Keywords Glossopharyngeal neuralgia · Radiosurgery · Craniofacial pain · Gamma knife

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Introduction

Glossopharyngeal neuralgia (GPN) represents a rare craniofacial disorder accounting for about 1% of all craniofacial pain syndromes [2]. Its incidence is much more rare than trigeminal neuralgia (TN; 1%) [2]. Clinically, GPN is characterized by unilateral and strong pain attacks located in the area of the base of the tongue, the posterior portion of the throat, the tonsillar fossa region and the angle of the jaw with irradiation on the deep portion of the ear canal [2, 22]. Pain is paroxysmal, lasting from seconds to few minutes, and may remit and relapse as for TN [2, 5, 22]. This area is innervated by both the XIth and the sensitive portion of the Xth cranial nerves, and according to this physio-anatomical data, some authors suggested the name vago-glossopharyngeal neuralgia [2, 4]. Triggering phenomena are swallowing, couching, chewing, speaking and yawing, and together with pain, sometimes GPN can be associated with cardiovascular manifestations, such as arrhythmias that can be potentially lethal [2, 16, 22].

The current diagnostic criteria for GPN according to the International Classification of Headache Disorders (ICHD, 3rd edition, 2013) are the following: (1) at least three pain attacks located in the abovementioned regions; (2) three or more of the following characteristics recurrent paroxysmal pain attacks lasting few seconds to 2 min—severe pain, shooting, stabbing of sharp pain—precipitated by swallowing, coughing, talking, or yawning; (3) no evidence of neurological deficits; and (4) pain syndrome not better accounted for another ICHD diagnosis [5].

In case of vagus nerve involvement, approximately 2% of cases, patients may also experience bradycardia, asystolia, syncope and seizures [20]. The most affected side in the left, with a left/right ratio of 3:2 [15].

GPN seems to share several features with the more common TN. It can be classified as idiopathic, in case of nonorganic dysfunction or neurovascular conflict (NVC), causing nerve compression to the root entry zone (REZ) [2, 4, 9, 10, 20].

As for TN, the mechanism of pain is related to demyelination and re-myelination processes, of which vascular nerve compression is only sometimes responsible [3].

Medical therapy and microvascular decompression (MVD), in case of vascular nerve compression, represented the mainstay of GPN management [22].

To date, other ablative therapies have been reported; however, because of the rarity of this pain syndrome, few data are available. Among the ablative procedures, gamma knife radiosurgery (GKRS) has been recently introduced in the management of GPN with good pain control and low complication rates.

The purpose of this study is to systematically review the available literature on GKRS for the management of GPN.

Material and methods

Search strategy

A systematic literature search was performed on Pubmed, Web of Science and Google Scholar by using the MeSH-terms "Glossopharyngeal neuralgia, Radiosurgery, Gamma Knife, Stereotactic radiosurgery".

Eligibility and exclusion criteria

Eligibility criteria were English-language publications and studies reporting GKRS treatment.

Exclusion criteria were no full-text documents, such as abstracts, no English language and no stereotactic radiosurgery or other radiation treatment.

Data selection and analysis

After initial screening by reviewing the full text articles, the selected publications were assessed for eligibility according to inclusion/exclusion criteria, and duplicated articles were excluded. Some additional studies were selected from articles and their references. By reviewing full text, three studies were excluded from the final analysis in order to avoid patients' duplication. Finally, the included papers underwent data extraction and analysis.

Figure 1 summarizes the review process.

Evaluation criteria

Pain response to GKRS has been standardized according to the Barrow Neurological Institute Pain Intensity Score (BNI) [10]. BNI Grade I was defined as pain-free without medication; BNI Grade II as occasional pain but off medication, BNI Grade IIIa as no pain with continued use of medications, BNI Grade IIIb as occasional pain controlled with medication, BNI Grade IV as pain improved but not adequately controlled with medication and BNI Grade V as no pain relief [10]. Favourable outcome was considered in case of BNI between I and IIIb at last reported follow-up.

Recurrence was defined as painful new event after a positive pain response to GKRS.

Adverse reactions to GKRS were classified as any neurological change from the pre-treatment clinical status.

Statistical analysis

IBM SPSS Statistics for Mac, version 22.0.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. Statistical significance was defined as $P = 0.05$. Categorical variables were compared with the two-sided Pearson χ^2 test and Fisher's exact test.

Results

A total of eight studies were included in the analysis process. All the selected studies were retrospective case series. Three studied were excluded, because the same patients were added to a multicentre study [10, 19, 27, 29]. Table 1 summarizes the literature review.

Patients' characteristics

Forty-two patients undergoing GKRS for GPN have been reported between 2005 and 2016. The mean reported age was 62 years (median 62, range 36–99); among these, 17 were male (40.47%) and 25 were female (53.53%; male-to-female ratio 0.68).

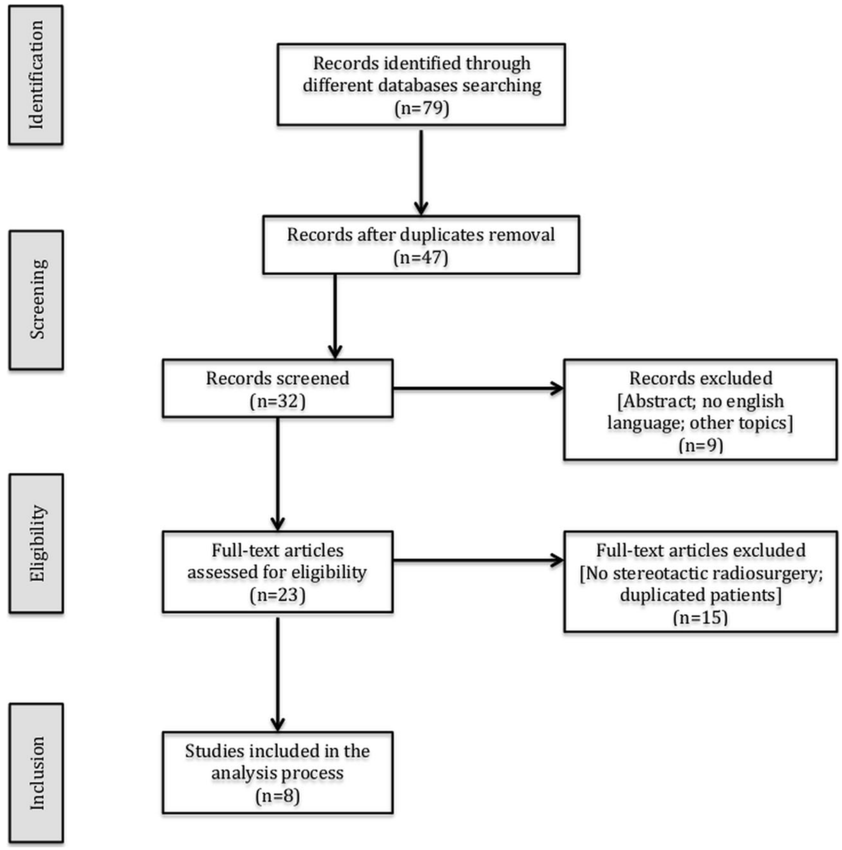
Data about the presence of NVC were reported in 30/36 cases: 24 patients presented NVC (66.6%), while 12 cases had no NVC on imaging studies (33.4%).

GKRS was performed after failure of previous medical therapy in 38/42 cases (90.5%); 1 patient (2.3%) underwent a nerve block procedure before GKRS; 4 patients underwent MVD (9.5%); 1 patient (2.3%) percutaneous rizothomy and 1 case (2.3%) balloon compression (Fig. 2).

Radiosurgical treatment

Two different targets have been considered for GKRS treatment. In 37/42 cases (88.1%), the distal portion of the glossopharyngeal nerve at the level of the glossopharyngeal meatus (GPM), whereas in 11.9% of cases (5/42), the cisternal part of the glossopharyngeal nerve (CIS) was targeted for the GKRS treatment.

Fig. 1 Flowchart search results



The mean reported maximal dose was 79.42 Gy (median 80, range 60–90).

In almost all cases, the dose was administered by using a single shot with a 4-mm collimator.

Outcome results

Follow-up data were available in all cases [19]. The average follow-up period was 27 months (median 23.5 range 6–83).

Outcome was reported for each single patient in 7/8 series (20 patients). At the last reported follow-up evaluation, patients were classified as BNI Grade I in 13 cases (65%), Grade IIIa in 4 cases (20%) and Grade V in 5 cases (15%). Additionally, Kano and colleagues in their series reported a favourable pain response (Grades I–III) in 16/22 cases (72.7%) and poor or no pain response (Grades IV–V) in 6/22 cases (27.3%) after GKRS. By applying this classification, the overall rate of favourable pain response was 78.6% (33/42), while poor response was reported in 21.4% of cases.

By analysing pain response and NVC (n = 14), among those with NVC, 77.7% of cases good response and 22.3% of cases poor response; whereas among those without NVC, 80% experienced good pain response and one case (20%) showed poor response.

Previous surgical treatments for GPN seemed not to influence response to GKRS, even if it is not possible to give definitive conclusions because of the few reported cases.

By analysing pain response and target type, poor outcome was reported in 40% of CIS target, whereas 18.9% experienced poor response in the GPM target group. It has to be noticed that CIS target failure group was treated with a dose of 70 Gy, while in the remaining three cases of CIS target with good outcome, the adopted dose was ≥80 Gy (χ^2 test $p = 0.174$).

By comparing dose and pain response, poor outcome was reported in 50% of cases treated with a dose <80 Gy, while in 16.6% of those patients treated with a dose ≥80 Gy, experienced poor pain response (χ^2 test $p = 0.065$; Fisher's exact test $p = 0.101$).

Data on pain recurrence were available in 36 patients. Recurrence was reported in 15 cases (41.6%). A statistical significance was found between pain recurrence and target type (χ^2 test $p < 0.001$); whereas, we did not find any statistical significance between pain response and target type (χ^2 test $p = 0.281$).

No adverse reactions were reported after single GKRS treatment. Two patients (4.7%) experienced hyperesthesia in the palatoglossal region after repeated GKRS for refractory pain, performed several months after the initial procedure [10].

Table 1 Literature review of published series of GKRS for GPN

Authors/year (*n*)	Age/sex	Side	Previous treatment	NVC	Target	Dose (Gy)	FU (months)	Outcome[a]	AE	PR	Notes
Stieber [28] (1)	N/A; F	R	MED	+	GPM	80	6	I	None	+	Pain-free 3 months; recurrence 6 months
Yomo [32] (2)	83; F	L	MED	+	GPM	60	50	I	None	+ (2 months)	New GKRS 7 months; 2 TC 10 and 10 months thereafter
	49; M	L	MED	−	GPM	75	12	I	None	−	−
Lévèque [13] (7)	83; F	N/A	MED	+	GPM	60	7	V	None	+	Repeated GKRS 7 months; TC 10 months
	62; M		MED	−	CIS	70	24	V	None	+	CS
	66; M		MED	+	CIS	70	24	V	None	+	MVD
	49; M		MED	−	GPM	75	32	I	None	−	−
	71; M		MED	+	GPM	80	13	IIIa	None	+	−
	36; F		MED	−	GPM	80	10	I	None	−	−
	65; M		MED	+	GPM	80	8	IIIa	None	+	−
O'Connor [16] (1)	99; F	L	MED	−	GPM	80	16	I	None	−	−
Martinez-Alvarez [15] (5)	56; F	N/A	MED	N/A	GPM	80	83	IIIa	None	−	PC 10 months
	73; F		MED; Rizo	N/A	GPM	90	71	I	None	−	PC 2 months
	62; F		MED; MVD	+	GPM	90	31	I	None	−	PC 6 months
	66; M		MED	N/A	GPM	90	19	I	None	−	PC 10 months
	37; F		MED; MVD	+	GPM	90	14	IIIa	None	−	PC 4 months
Heroux [6] (1)	43; M	L	MED	+	GPM	80	44	I	None	−	−
Xiong [31] (3)	88; F	R	MED	N/A	CIS	80	28	I	None	−	PI 2 days
	51; F	L	MED	N/A	CIS	80	25	I	None	−	PI 7 days
	56; M	R	MED	N/A	CIS	86	23	I	None	−	PI 11 days
Kano [10][b] (22)	60[c]; 8; M 14; F	15L 7 R	2 MVD; 1 BC; 18 MED; 1 NB	15/22	GPM	80[c]	45[c]	16 I–III; 6 IV–V	2/22[e]	8[d]	5 new SRS; 2 MVD; 2 NS

NVC neurovascular conflict, *FU* follow-up, *PR* pain recurrence, *F* female, *M* male, *mos* months, *N/A* not available, *L* left side, *R* right side, *GKRS* gamma knife radiosurgery, *MED* medical therapy, *Rizo* percutaneous rizothomy, *BC* balloon compression, *NB* nerve block, *CIS* cisternal nerve portion, *GPM* glossopharyngeal meatus, *TC* thermocoagulation, *CS* cortical stimulation, *PC* pain control after, *PI* pain improvement after, *NS* nerve section, *SRS* stereotactic radiosurgery

[a] According to the Barrow Neurological Institute Pain Score

[b] 22 patients

[c] Median values

[d] Among 16 patients BNI I–III

[e] 2 hyperesthesia in the palatoglossal region after repeated GKRS

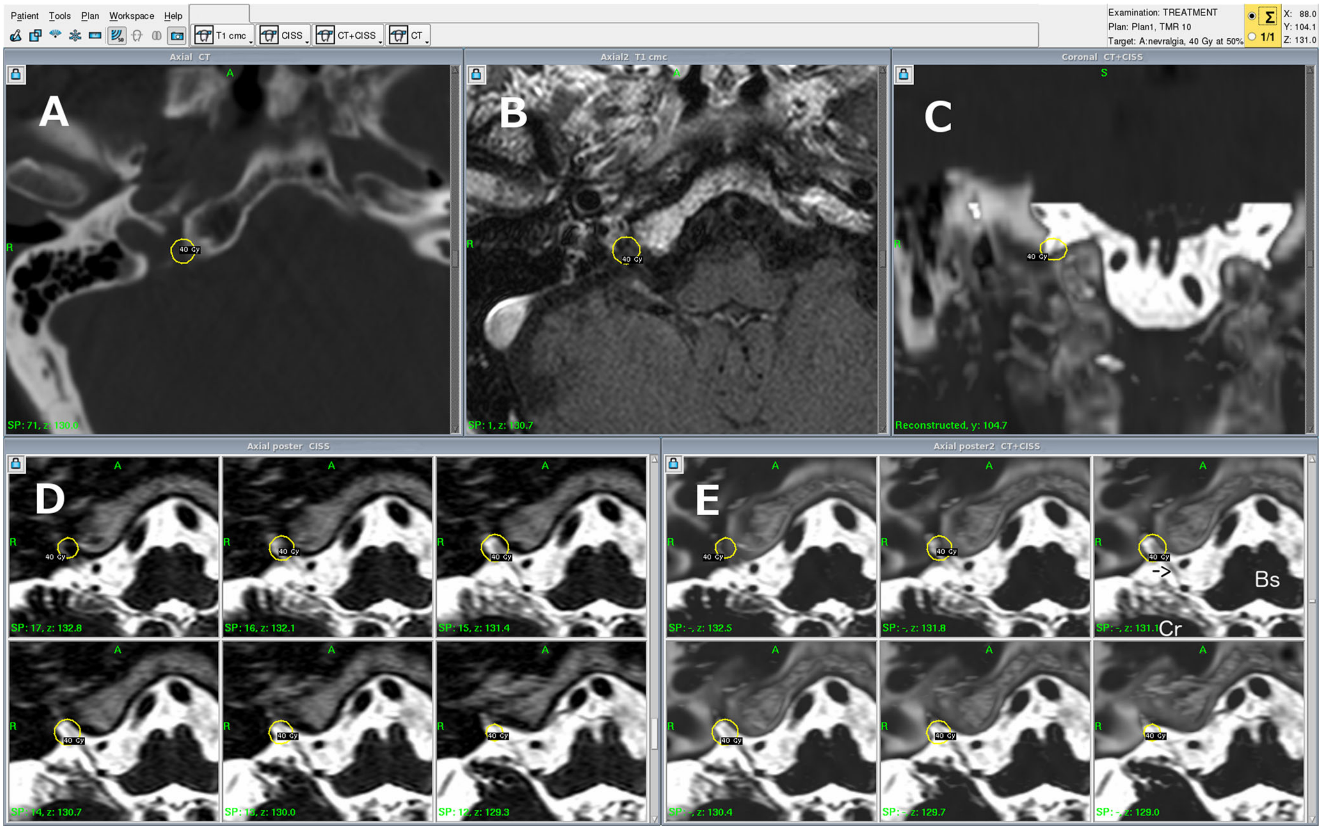


Fig. 2 GKRS treatment planning. Axial bone-windowed CT image showing the glossopharyngeal meatus (**a**). T1-weighted contrast enhanced MRI acquisition (**b**). Coronal three-dimensional constructive interference in steady-state (CISS) MRI merged with bone-windowed CT acquisition, showing the glossopharyngeal meatus (**c**). Axial CISS MRI, showing the treatment planning and the relevant dosimetry to the nerve (**d**). Axial CISS MRI merged with bone-windowed CT scan showing the relevant anatomy and the neurovascular conflict (*black arrow*) (**e**). *Bs* brainstem, *Cr* cerebellum

Discussion

GPN is a rare craniofacial pain syndrome characterized by paroxysmal and usually unilateral pain attacks in the region of the ear, base of the tongue, tonsillar fossa and the angle of the jaw lasting from few second to any minutes [5, 14]. GPN shares some clinical features with the most common TN. Pain attacks are precipitated by some actions, such as swallowing or chewing; multiple attacks per day, up to 40, may jeopardize patients' quality of life [5].

The actual incidence of GPN is reported between 0.2 and 1.3% of all craniofacial pain disorders; however, the real incidence may be underestimated, because GPN is often misinterpreted or is not considered in the differential diagnosis of craniofacial pain syndromes [2, 14, 20].

Some authors found a correlation between the nerve length and central myelin volume and the incidence of cranial neuralgias [4]. For glossopharyngeal and vagus nerves, authors reported a smaller length and volume if compared to the trigeminal nerve: this paradigm explained why GPN is less common than TN [4].

Similarly to TN, GPN can be classified as idiopathic cases, related or not to a vascular compression to the IXth–Xth nerve complex by the posterior-inferior cerebellar artery (PICA); otherwise, secondary cases caused by intracranial disorders (such as aneurysms, cerebellopontine angle lesions, persistent hypoglossal artery, petrositis) and extracranial diseases (oropharynx tumours, tonsillitis trauma, vertebral artery dissection and stylohyoid ligament ossification and elongated styloid process) and Chiari malformation [2, 4, 8, 14, 21–24].

According to these characteristics, an imaging study is mandatory in the management of patients experiencing GPN to differentiate idiopathic and secondary forms [22].

Magnetic resonance imaging and magnetic resonance angiography are indicated in order to visualize mass or vascular lesions, which may be responsible for GPN [2, 7, 22, 24].

Moreover, CT scans can help to visualize an ossified and elongated stylohyoid ligament, which can cause secondary GPN in the Eagle syndrome [1, 25].

Antiepileptic drugs, such as carbamazepine, represent the mainstay of GPN treatment; however, they can show some side effects or fail in controlling pain over time as in the experience of TN treatment [5, 20, 22].

In these cases, some other treatment options are available. MVD is considered in those cases related to PICA or other neurovascular compression [2, 22–24]. MVD represents a physiologic treatment option if compared to others ablative techniques, as reported in the management of TN, providing pain relief in more than 90% of patients, with low recurrence rates [2, 22]. However, after MVD patients may experience partial or no pain relief, even if the rate of unsatisfactory surgical outcome is quite low [2]. Long-term failure rate of MVD ranged between 0 and 24% of cases; however, these data are not always reported in surgical series [2, 9, 15, 17]. In a recent series, long-term complete pain relief rate (>2 years) was of 94.4% [22]. MVD carried a risk of permanent cranial nerve deficits depending on the series, such as hearing loss, and the common complications of open surgical procedures [2, 22].

Together with MVD, intracranial or extracranial surgical section of the glossopharyngeal nerve has been proposed for the management of GPN [2]. These techniques, despite the high rates of short-term pain relief, are related to a high rate of recurrence and major complications [2, 22].

Another less common reported technique is the trigeminal tractotomy-nucleotomy [11, 22]. Despite this technique, provided quick pain control in almost all cases, less than 20 patients have been reported to date, and it is not possible to draw definitive conclusions on its efficacy and safety [22].

Additionally, percutaneous ablative techniques have been also applied for GPN [2]. Percutaneous radiofrequency thermocoagulation (PRT) is a well-known technique TN treatment [2]. Contrarily to TN experience, PRT for GPN is more difficult to perform, because the complex neurovascular anatomy is related to this region; the rate of damage to the adjacent vessels is high if compared to PRT for TN [2]. Despite the good outcome in terms of pain control, PTR presented a high risk of vocal cord paralysis and dysphagia meaning that it has to be considered only in very selected cases [2].

Among the ablative procedures, GKRS represents an emerging treatment option for GPN. GKRS is a well-known option in the management of TN with good outcome rates in terms of pain control and low complications [12, 18, 30]. GKRS has been introduced in the management of GPN in the 2005, and to date, a total of 42 patients have been reported [6, 10, 13, 15, 16, 28, 31, 32].

Pain control has been reported in the majority of cases, with a low complication rate (no complications after one treatment and 4% after a repeated GKRS) and a pain recurrence rate accounting for about 40%.

Martinez-Alvarez and colleagues recently, reporting a concomitant case of TN and GPN both successfully treated by GKRS, stated that the two pain syndromes share a common pathophysiology, and therefore, response rates are comparable [15].

However, the interval between GKRS and pain response seemed to be shorter than TN, and these data may reflect the low number of GKRS cases or, in our opinion, the fact that by using similar doses of TN for GPN, the smaller size of the target may be responsible for this short interval [3, 4, 15, 32].

In most of the series, the GPM was targeted, while in only 11.9% of cases, the target was considered the CIS. Lévêque reported that the selection of the target was influenced by the radiation exposure of the brainstem, while other authors considered the GPM as the primary target of the radiosurgical treatment [6, 10, 13, 15, 16, 19, 27, 29, 31, 32]. GPM can be well visualized by merging MR and CT imaging, and targeting the GPM seemed to be related to better outcome, allowing for a minor radiation exposure to the brain stem [10, 13, 16]. Moreover, the target has to include both the glossopharyngeal and vagal meatus, in order to improve the chances of a good pain response to GKRS [19, 32].

Previous surgical therapies did not influence pain response to GKRS for GPN, whereas these relationships in GKRS for TN are still controversial [12, 18, 26, 30].

As for TN, MVD for GPN is related to high pain control and low recurrence rates both at short- and long-term follow-up periods.

At present, there is no consensus on the treatment dose for GPN [13]. Some authors stated that the treatment dose has to be ≥75 Gy, because it seems to be related to a higher rate of response and a longer pain-free interval [13, 15, 28]. Our review confirmed these data, showing that when the treatment dose is <80 Gy, one half of patients experienced a poor outcome, while this result decreased to less than 20% with a treatment dose ≥80 Gy. Additionally, these findings have been already reported in in the GKRS-TN literature, where the recommended dose ranges between 70 and 80 Gy [12, 18, 26, 30].

Martinez-Alvarez reported four cases treated with a dose of 90 Gy, with no side effects after a mean follow-up period of 33.75 months [15]. For TN, doses ≥90 Gy are occasionally related to a higher pain response; however, they are associated with a higher morbidity rate [12, 30].

For GKRS series, outcome data are not homogeneously reported, making it difficult to compare results from different series. By applying the same criteria for pain control, a favourable pain response has been reported in 78.6% of cases, and among these patients, recurrence has been reported in 41.6% of cases.

One of the potential limitations of GKRS is the long-term pain control [12, 18, 26, 30].

In the largest series by Kano et al., pain recurrence was reported in the 50% of cases of patients experiencing a good pain response after GKRS treatment, after a mean follow-up of 45 months [10]. Stieber and colleagues stated that the suboptimal radiation of the entry zone in the jugular foramen was probably responsible for the pain recurrence 6 months after GKRS. In the remaining cases, recurrence has been reported from 2 to 24 months after GKRS. We found a statistical significance between pain recurrence and the type of target type while a trend toward significance between dose and pain response. Longer follow-up and larger cohort are needed to better outline the efficacy and safety of GKRS for GPN.

The results in terms of pain control period are not comparable to the TN experience because of the few cases reported to date for GPN; however, the long-term efficacy of GKRS for pain control is a common issue with GKRS for TN [12, 18, 26, 30].

Conclusion

GKRS represents a valuable option for the management of GPN. Pain control and complication rates are better than those reported by other ablative procedures and MVD; however, the long-term efficacy of GKRS is not entirely defined. Further studies are needed to assess the optimal radiosurgical strategy and the long-term results.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required.

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