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Gamma-knife radiosurgery for jugular foramen schwannomas. A systematic review and meta-analysis

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ABSTRACT

Introduction: Jugular Foramen Schwannomas (JFS) have been traditionally treated with surgical resection with an associated significant post-operative morbidity. Stereotactic radiosurgery has been investigated as potentially minimally invasive alternative to microsurgery. The aim of this study was to provide a systematic review and meta-analysis of the available literature regarding the outcomes of cases of JFS treated with radiosurgery.

Methods: A literature review until 28th of March 2023 was performed. All studies looking at the outcomes of radiosurgery for the treatment of JFS were included. Studies including non-vestibular schwannomas without clear distinction of the tumour type were excluded. Risk of bias was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) scale.

Results: Eight (8) studies with a total of 375 patients met the inclusion and exclusion criteria and were included in the analysis. Pooled overall tumour control rate was 93.2 % (95 % CI 89.8–96.6) after a weighted mean follow-up of 54.07 months (95 % CI 46.8–61.3). Patient free survival was reported only in 4 studies and ranged from 87 % to 97 % and 76.9–93.8 % in 5 and 10 years respectively. The radiation induced cranial nerve deficits rates after GKRS were 3.6 % (95%CI 1.7, 5.5 %).

Conclusion: According to our findings, radiosurgery for JFS has favourable clinical outcomes with a high rate of long-term tumour control and low complication rates.

1. Introduction

The vast majority of intracranial schwannomas arise from the eighth nerve, with schwannomas originating from other cranial nerves being extremely rare. Jugular foramen schwannomas (JFS) account for 2.9%–4% of all intracranial schwannomas and they are the third most common benign brain tumour.[1] These tumours may arise from any nerve of the jugular foramen including the glossopharyngeal, vagus, or spinal accessory nerve, but frequently identifying the absolute origin of the lesion is only possible intra-operatively.[2] JFSs are usually diagnosed late after patients gradually develop lower cranial nerve (CN) deficits. To date, surgical resection has been the first line treatment for patients with JFS.[3] Given their anatomical features and the close proximity to surrounding neurovascular structures, surgical resection is frequently associated with development of new neurological deficits post operatively. Despite recent advances in skull base surgical techniques, complete removal of JFS without any associated neurological complications remains a challenge.[4]

Stereotactic radiosurgery (SRS) is known to provide excellent tumour control rates with good functional outcomes for vestibular schwannomas (VS), but given the rarity of non-vestibular schwannomas, its efficacy in the treatment of JFS has yet to be established. Recently, a few studies have shown the potential of SRS as a valid alternative treatment modality to microsurgical resection, particularly for small-to medium-sized JFSs or as an adjuvant therapy for residual or recurrent lesions. It is well established that after treatment with SRS for non-vestibular schwannomas, cranial nerve function can be preserved in most cases.[5] Tumour control rates using SRS are similar between vestibular and non-vestibular schwanomas suggesting that vestibular and nonvestibular schwannomas have a similar biologic response to radiation. Also, nonvestibular schwanomas resection can be challenging resulting in significant cranial nerve morbidity with postoperative cranial nerve deteriorations typically reported in 30%–93 % of patients.[6]

The aim of this article is to provide an overview of the existing literature through a systematic review of this novel trend on the treatment of JFS. To the best of our knowledge, this is the first study that provides an overview of the outcomes and complications of JFS treated with GKRS.

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Abbreviations

CN	Cranial nerve
GKRS	Gamma Knife Radiosurgery
JFS	Jugular foramen schwannomas
LINAC	Linear accelerator based stereotactic radiosurgery
PFS	Progression Free Survival
SRS	Stereotactic radiosurgery
VS	Vestibular schwannomas

2. Methods

2.1. Search strategy

A systematic search using the PubMed, Embase, and Cochrane databases until 28th of March 2023 was conducted by two independent reviewers (TS and GA), following PRISMA guidelines and recommendations.[7] The following medical subject headings (MeSH) and free text were used: "gamma knife" OR "stereotactic radiosurgery" AND "jugular foramen schwannoma" OR "non vestibular schwannomas." The reference lists of all relevant studies were also manually double checked to identify additional eligible studies that might have been missed during the initial electronic search.

2.2. Inclusion and exclusion criteria

Studies that met the following criteria were included: (1) Included patients with a diagnosis of JFS, (2) Use of GKRS as the primary treatment modality (3) Minimum of 6 months follow up.

The exclusion criteria were as follows: (1) Insufficient cohort of patients (number of patients <8), (2) any non-English studies or articles involving non-human subjects, (3) Conference abstracts. To further reduce heterogeneity, we excluded articles that use Linear accelerator based stereotactic radiosurgery (LINAC) as primary treatment modality.

After removing duplicate publications, two reviewers (TS and GA) independently assessed the title and abstract relevance. If the publication was selected by either reviewer, a further review of the full text was required. Any dispute was resolved by consensus.

Tumour control after GKRS was defined as "stable" or "decreased" tumour size in follow up imaging. Adverse radiation effects were defined as new CN deficit not directly related to tumour growth.

Primary outcomes of our study were tumour control rates, new cranial nerve deficits rates post GKRS and Progression Free Survival (PFS) rates. Tumour control rates were defined as either tumour stability or tumour regression. Publication bias was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group system.[8] The potential risks of bias considered included selection bias, performance bias detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (clear inclusion and exclusion criteria.) Low bias studies were the prospective studies or the retrospective studies with large effects and no obvious bias.

2.3. Statistical analysis

Weighted summary rates were determined using meta-analysis models. Testing for heterogeneity was performed for the meta-analysis. The OpenMeta Analyst (Agency for Healthcare Research and Quality) and Rev-man (Review Manager Version 5.4. The Cochrane Collaboration, 2020) were used for statistical analysis[9] A random-effects analysis was used to calculate the pooled estimates. The results of each study were expressed as binary proportions with 95 % confidence intervals (CIs).

3. Results

3.1. Literature search

Initial search identified 141 studies. Two additional studies were identified after manually searching the references of the included studies. After excluding duplicates and careful screening, 50 studies were retrieved for full-text analysis on the basis of the title and abstract. 12 studies were excluded with detailed analysis of the reasons showed in Table 1. Eight studies which met our inclusion and exclusion criteria were finally selected for analysis (Fig. 1).

3.2. Risk of bias

A detailed table with justification of the GRADE assessment is provided on Table 2. Based on the GRADE assessment, the performance bias was low in 5 sutdies[23,24,26,27,29] and unclear in one study.[28] Detection bias was low[24,27] and unclear in three studies.[25,3,29] Attrition bias was low in the majority of the included studies.[23,24,25,27,28,3,29] Detection bias was high only in two studies[23,26,27] and unclear on 4 studies.[25,28,3,29] Reporting bias was low in 5 studies.[23,24,26,3,29] There were also other sources of bias reported across studies with the main being small sample and retrospective design.

4. Results

Eight studies involving 375 patients who had undergone GKRS for the treatment of JFS were included in the analysis. The mean margin dose ranged from 12 to 15 Gy. The 51.6 % of the cases (95 % CI 46.5%–56.7 %) had undergone prior microsection before GKRS. Tumour volume was only reported in 5 studies and it ranged from 2.9 to 5.7 cm^3. Type A (as per Pellet et al[30] classification) was the most frequently encountered tumour type with its frequency ranging from 24 % to 76 % (Table 3).

Pooled overall tumour control rate was 93.2 % (95 % CI 89.8–96.6), after a weighted mean follow-up of 54.07 months (95 % CI 46.8–61, $I^2 = 42.54$) The vast majority of the patients undergoing GKRS for JFS have a degree of pre-existing neurological compromise. We looked at the new CN deficits that were directly attributed to the radiation effects and were evident at the final follow up. The random effects pooled rate of new CN deficits was calculated at 3.6 % (95%CI 1.7, 5.5 %, $I^2 = 0.974$). Transient neurological deficits which recovered were not taken into account. Patient free survival was reported only in 4 studies and ranged from 87 % to 97 % and 76.9–93.8 % in 5 and 10 years respectively. In terms of additional treatment after GKRS, only 18/345 patients required further management, with 7 patients undergoing microsurgical resection and 11

Table 1
Studies excluded with reasons.

Study name	Reason for exclusion
Showalter et al 2008[10]	-Pooled results with non acoustic schwanomas -Small sample
D'Astous et al 2017[11]	-Pooled results with non acoustic schwanomas
Langlois et al 2018[12]	-Small sample ($n = 5$)
Bansal et al 2022[13]	-Case report
Safavi-Abbasi et al 2010[14]	-Pooled results with non acoustic schwanomas -Small sample
Choi et al 2011[15]	-Pooled results with non acoustic schwanomas -Small sample
Kida et al 1995[16]	-No full text in English available
Mabanta et al 1999[17]	-LINAC
Kimball et al 2011[18]	-Pooled results with non acoustic schwanomas
Elsharkawy et al 2012[19]	-Pooled results with non acoustic schwanomas
Ruangkanchanasetr et al 2016[20]	-Conference abstract
Myeongjong Kim et al 2018[21]	-Conference abstract
Langlois et al[22]	-Small sample
Zoo et al[36]	-CyberKnife

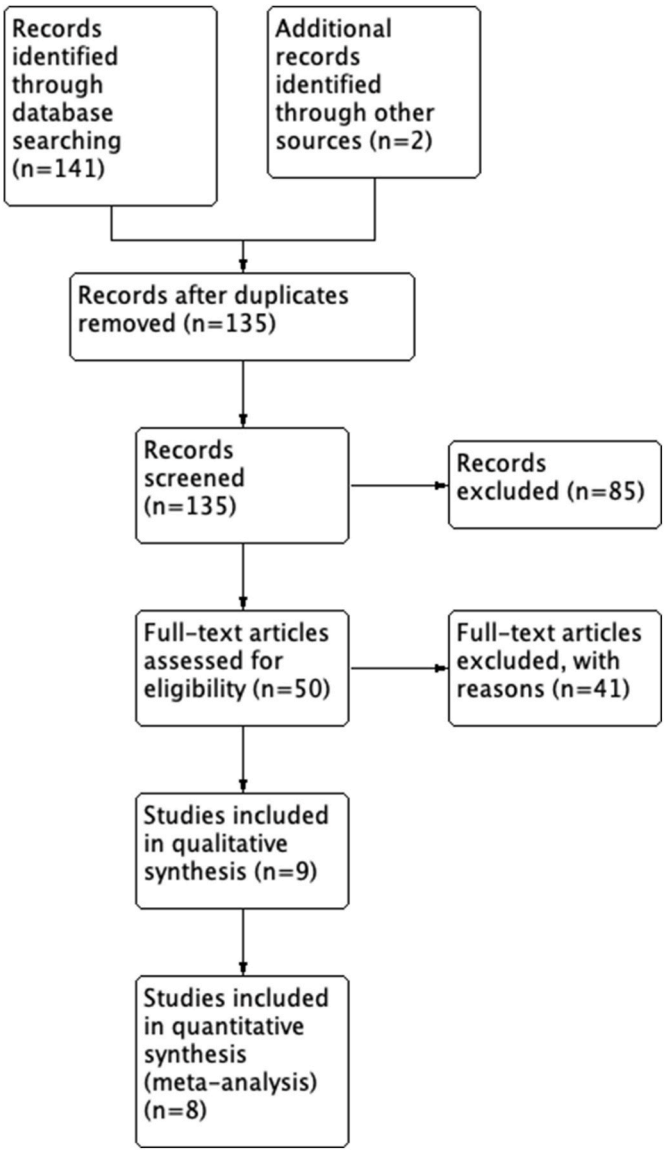

Fig. 1. Flow diagram of the included studies.

patients having a repeat GKRS procedure (Table 3).

5. Discussion

During the last two decades, GKRS has emerged as a possible alternative treatment option to microresection of JFS. Given the rarity of the disease, the published reports on the efficacy and safety of GKRS are only based on studies with small number of patients. To the best of our knowledge, this is the first review to assess the outcomes of GKRS treatment in JFS in a large cohort of patients. According to our results, the tumour control rate was 93.2 % with a mean follow-up period of 54 months. This figure is comparable with that of vestibular schwannomas, with their tumour control rates after radiosurgery being calculated at 96.2 % in a large study in Netherlands.[31]

The other treatment option is microsurgical resection of JFS. There are relatively high rates of gross total resection in recent studies that range between 31 and 100 % (mean 90 % mean 71.7 %)[32] The main drawback related to surgery is lower cranial nerve dysfunction post operatively. This can have a significant impact on quality of life, leading often to airway compromise and swallowing difficulties. While some patients experienced CN deficits immediately after surgery IX-X nerve

Table 2
Risk of bias judgement assessment of the included studies.

study	Criteria	Strength	Concern	Risk of bias
Kano et al 2018[23]	Selection bias		Unclear selection criteria. Retrospective design	High
	Performance bias	Clear radiosurgery technique protocol		Low
	Detection bias	All patients were evaluated by MRI at intervals of 3–6 months after radiosurgery	Follow up was <12 months for some patients Some patients did not have histological diagnosis of the tumour	High
	Attrition bias	There is no mention of loss to follow-up since the outcome assessment was performed		Low
	Reporting bias	The article appears to report all the measured outcomes without selective reporting		Low
Kim et al 2022[24]	Selection bias	Clear selection criteria. Exclusion criteria clearly defined (NFII or previous SRS) Retrospective design		High
	Performance bias	Clear SRS protocol		Low
	Detection bias	All patients underwent the first follow-up MRI within 6 months after SRS		Low
	Attrition bias	No missing data		Low
	Reporting bias	The article appears to report all the measured outcomes without selective reporting		Low
Peker et al 2012[25]	Performance bias	The participants were selected based on specific criteria related to SRS for JFS	Unclear exclusion criteria	High
	Detection bias		Unclear blinding of outcome assessors.	Unclear
	Attrition bias	There is no indication in the article of any missing data		Low

(*continued on next page*)

Table 2 (*continued*)

study	Criteria	Strength	Concern	Risk of bias
	Reporting bias		PFS 5–10 % are not reported	High
			Small sample, retrospective design	High
Hasegawa et al 2016[26]	Selection bias		Retrospective design	High
	Performance bias	Clear description of radiosurgery protocol	5 patients were treated with 3 session GKS	Low
	Detection bias		Unclear blinding of the outcome assessors	High
			Half of patients did not have histological diagnosis of the tumour	
	Attrition bias		Some patients were lost to follow up at 5 or 10 years	High
	Reporting bias	The article appears to report all the measured outcomes without selective reporting.		Low
	Other sources of bias		Retrospective study; patient selection, the radiosurgical techniques and follow-up imaging varied between centers	High
Zhang et al 2002[27]	Performance bias	Clear description of radiosurgery protocol	Retrospective study	Low
	Detection bias		Unclear blinding of the outcome assessors	High
	Attrition bias			Low
	Reporting bias	The article appears to report all the measured outcomes without selective reporting		Low
Shinya et al 2021[28]	Performance bias		Unclear selection criteria	Unclear
			Retrospective design	
	Detection bias		Unclear blinding of outcome assessors.	Unclear
	Attrition bias	There is no indication in the article of any missing data		Low
	Reporting bias		PFS, Imaging progression are not reported	High
	Other sources of bias		Single-institution, retrospective analysis. Small sample size	High
Muthukumar et al 1999[3]	Performance bias	Consistent radiosurgical protocol		High
	Detection bias		Unclear blinding of outcome assessors.	Unclear
	Attrition bias	There is no indication in the article of any missing data		Low
	Reporting bias		PFS 5,10 % are not reported	Low
	Other sources of bias		Small sample, retrospective design	High
Martin et al 2007[29]	Performance bias	Consistent radiosurgical protocol		Low
	Detection bias		Unclear blinding of the outcome assessors	Unclear
	Attrition bias	None of the patients were lost to follow up		Low
	Reporting bias	The article appears to report all the measured outcomes without selective reporting.		Low
	Other sources of bias		Small sample, retrospective design	High

dysfunction ameliorated compared with the immediate post op period in most of the patients (9 out of 14 patients).[34] Sedney et al has suggested a less aggressive technique for removal of the tumour and found that it is associated with less complications rates but higher recurrence rates.[33] In a study looking at long term outcomes after surgical resection of JFS, tumour regrowth was observed in 9 of 15 patients at 6–89 months (mean, 31.2 months) after surgery.[34] The main benefit of surgical resection that it is still the preferred treatment for large tumours with brain stem compresssion. In our study, preoperative tumour volume ranged from 2.9 to 5.7 cm^3. This is significantly less than a series of patients with JFS treated with surgical resection which was 7.08 cm^3.[35] In our cohort of patients, only 18/345 patients required additional treatment in the form of surgery or repeat GKRS.

Although GKRS is considered a relatively safe procedure, radiation induced adverse effects have been reported in literature. In our study, the pooled complication rate that was not attributed to tumour progression was calculated at 3.6 % (95%CI 1.7, 5.5 %). Very rarely, patients can present with more serious complications. Kawashima et al for example, described a case that developed intra-tumoral haemorrhage associated with hearing loss and headache after undergoing GKRS for JFS.[36] Shinya et al[28] explored the association between the radiation dose and the incidence of adverse events post GKRS. The authors found that a prescribed dose of >12 Gy was significantly associated with increased risk of CN injuries (odds ratio [OR], 7.79; 95 % confidence interval [CI],

Table 3
Patient's demographics, tumour type classification and outcomes after GKRS treatment.

study	cases	men	age	mean f/u after (months)	tumour volume (cm3)	mean max radiation (Gy)	Prior microsurgery (%)	Grade Rating	A (%)	B (%)	C (%)	D (%)	Additional management (no of patients)	Adverse radiation effects (%)	PFS 5 %	PFS 10 %	Imaging stable (%)	Imaging decreased (%)	Imaging progress (%)
Kano et al 2018[23]	92	44	48	51	4.1	12.5	41 (44.5)	Low	43 (47)	15 (16)	7 (8)	27 (29)	6 (repeat GKRS), 4 (surgery)	7.6	87	82	33 (36)	47 (51 %)	12 (13 %)
Kim et al 2022[24]	46	18	49.5	50	3.9	13	15 (32.6)	Low	16 (34.8)	3 (6.5)	9 (19.6)	18 (39.1)	na	10.9	93.8	76.9	14 (30.4)	28 (60.9)	4 (8.7 %)
Peker et al 2012[25]	17	8	44	64	5.9	13	12 (70.6)	Very low					na	0	na	na	4 (23.6)	13 (76.4)	na
Hasegawa et al 2016[26]	117	51	53	52	4.9	12	61 (52)	Moderate	28 (24)	38 (32)	12 (10)	39 (33)	3 (surgery) 3 (GKRS)	3.4	89	83	42 (36 %)	62 (53 %)	13 (11 %)
Zhang et al 2002[27]	27	NA	NA	38.7	NA	14.6	NA	Very low	na	na	na	na	na	0	na	na	13 (48.1)	11 (40.7)	1 (3.7)
Shinya et al 2021[28]	25	13	49.1	58.4	5.7	13.1	14 (58.3)	Very low	na	na	na	na	na	8	na	na	na	na	na
Muthukumar et al 1999[3]	17	11	50	42	NA	15	13 (76.4)	Very low	13(76)	0	1 (6)	3 (17.6)	1 (surgery)	0	na	na	8 (47.05)	8 (47.05)	1 (5.8)
Martin et al 2007[29]	34	18	NA	83	NA	14	22 (64.7)	Low	26 (76.5)	1 (2.9)	1 (2.9)	7 (20.6)	1 repeat GKRS	0	97	94	16 (47.05)	17 (50)	2 (5.8)

3.1–19.5; $p < 0.001$). Kim et al[24] showed that 13 of 16 patients with early adverse events recovered with short course of intravenous or oral corticosteroids, with the mean resolution time being six months.

In our study PFS was found to be relatively high ranging from 87 % to 97 % and 76.9–93.8 % in 5 and 10 years respectively. Kano et al[23] suggested that dumbbell tumours had worse PFS because of their larger volumes and the lower margin doses that were treated with. They also found that dumbbell-shaped tumours were significantly associated with a higher rate of symptomatic deterioration. Non–dumbbell-shaped tumours are recognized at an earlier stage, which facilitates earlier and more successful intervention with SRS. They also identified a statistically significant correlation between the 5-year PFS and preoperative tumour size with the cut off being estimated at $\geq$ 6 cm3.

LINAC is another radiosurgical modality used in the treatment of non-vestibular schwanomas. There are very few reports in literature looking at the management of JFS with LINAC. Kimball et al[18] conducted a retrospective analysis of 16 patient with JFS that received LINAC. Local tumour control rate was calculated at 100 % and 86 % at 1 and 5 years respectively. In terms of adverse events post treatment, there was only 1 reported case that developed persistent numbness which was maintained at 4 years after radiosurgery. Mabanta et al[17] looked at 18 patients with non-vestibular schwannomas, out of which 9 were diagnosed with JFS and had received treatment with LINAC. This study only provided overall outcomes on non-vestibular schwannomas without focusing primarily on JFS. With a mean follow up of 32 months, all patients were alive and free of disease progression.

A very recent study from Zoo et al[37] showed that Hypofractionated stereotactic radiotherapy (HSRT) could offer better preservation of normal structures compared to single-fraction stereotactic radiosurgery. In 74 patients with JFS treated with HSRT over a 10 year period, the 5-year progression-free survival rate was particularly high at 93.2 %. Interestingly, out of the 73 patients with pre-existing cranial nerve neuropathies only 14 patients showed symptomatic deterioration.

6. Limitations

The main limitation of this study is related to the observational studies that were included in the analysis, which are mainly based on small cohort of patients. Also, the majority of studies included in this meta-analysis were retrospective. The absence of clinical trials introduces significant bias risks. This is on of the main reason that PFS was assessed only in a minority of studies. For this reason, follow up was inconsistent between studies with the length of follow-up for some of the patients being less than 12 months, thereby making it difficult to determine the effect of treatment versus the natural history of a skull base tumor such as a JFS. There were also some drawbacks related to the methodology of the included studies that contributed to the heterogeneity of the results and this included varied follow up period and diverse definition of tumour control. None of the included studies determined a set cut off in terms of tumour volume increase that would indicate radiological post operative tumour progression or regression.

7. Conclusion

In summary, the reported data suggest that patients with JFS treated with GKRS have excellent tumour control rates and PFS. Given the acceptable low risk of neurological deterioration following SRS, GKRS is a reasonable alternative to surgical resection for small-to medium-sized JFS. Future studies looking at outcomes of alternative radiosurgical modalities like LINAC and HSRT could further help expand our knowledge on minimally invasive management options for JFS.

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Timoleon Siempis: Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Spyridon Voulgaris:** Writing – review & editing, Supervision, Formal analysis. **George A. Alexiou:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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