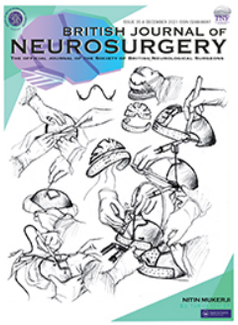

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RESEARCH ARTICLE

Stereotactic radiosurgery for cerebellopontine meningiomas: a systematic review and meta-analysis

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ABSTRACT

Objective: To (1) measure surgical outcomes associated with stereotactic radiosurgery treatment of cerebellopontine angle meningiomas, and (2) determine if differences in radiation dosages or preoperative tumor volumes affect surgical outcomes.

Methods: A systematic search was performed on the PubMed, Medline, Embase and Cochrane Library databases searching for patients under stereotactic radiosurgery for meningiomas of the cerebellopontine angle. After data extraction and Newcastle-Ottawa scale quality assessment, meta-analysis of the data was performed with Review Manager 3.4.5.

Results: In total, 6 studies including 406 patients were included. Postprocedure, patients had minimal cranial nerve complications while having an overall tumor control rate of 95.6%. Complications were minimal with facial nerve deficits occurring in 2.4%, sensation deficits of the trigeminal nerve in 4.0%, hearing loss in 5.9%, hydrocephalus in 2.0% and diplopia in 2.6% of all patients. Individuals with tumors extending into the internal auditory canal extension did not have significantly increases in hearing loss. There was a higher likelihood of tumor regression on postprocedure imaging in studies with a median prescription dose of >13 Gy (RR 1.27 [95% CI 1.04–1.56, $p = 0.0225$). There was no evidence of publication bias detected.

Conclusions: Radiosurgery is an effective modality for offering excellent tumor control of CPA meningiomas while allowing for only minimal complications postprocedure. A higher prescription dose may achieve higher tumor regression at follow up. Future studies should aim at establishing and optimizing accurate dosimetric guidelines for this patient population.

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Introduction

Meningiomas are the most common tumor of the CPA after vestibular schwannoma.[1–3] As these tumors increase in size, they can often cause symptoms of tinnitus, hearing loss, dizziness, trigeminal dysfunction, neurocognitive impairment and can begin to compress vital structures.[1,4,5] Since their anatomic location is in close proximity to intricate neurovascular structures such as cranial nerves, the basilar artery and the cerebellum, resection proves to be surgically challenging.[6,7] SRS has emerged in the last 20 years as an effective option for providing alternative and adjuvant treatment for low-volume meningiomas of the skull base in addition to microsurgery.[8,9]

Initial reports suggested that SRS was an excellent method of treatment for its ability to preserve the patient's hearing ability, facial nerve function and trigeminal nerve function while also providing excellent rates of tumor control.[10–12] This was also noted for meningiomas that develop extension into the IAC.[11] Thus, like other neurosurgical pathologies that are treated with SRS, establishing appropriate radiation dosages for this patient population has received considerable attention in the literature.[10,11,13–16] Radiation dosages are a modifiable factor that should be optimized for reducing postprocedural morbidity while also achieving high rates of tumor control.

Therefore, the purpose of this study was to measure rates of postprocedural morbidity associated with SRS treatment of CPA meningiomas. An additional goal was to measure how increased radiation dosages or preprocedural tumor volumes affect surgical outcomes. To answer these questions, a systematic review of the literature was performed of studies measuring rates of tumor control, hearing loss, facial nerve deficits, trigeminal nerve deficits, and other complications of surgery among patients undergoing SRS treatment of CPA meningiomas. Extracted data was then analyzed through a meta-analysis approach of published data.

Methods

Literature search strategy

A systematic review and meta-analysis of the extracted data was conducted according to the guidelines set by PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses).[17] The databases of Medline, PubMed, Embase and the Cochrane Database of Systemic Reviews was searched using the following

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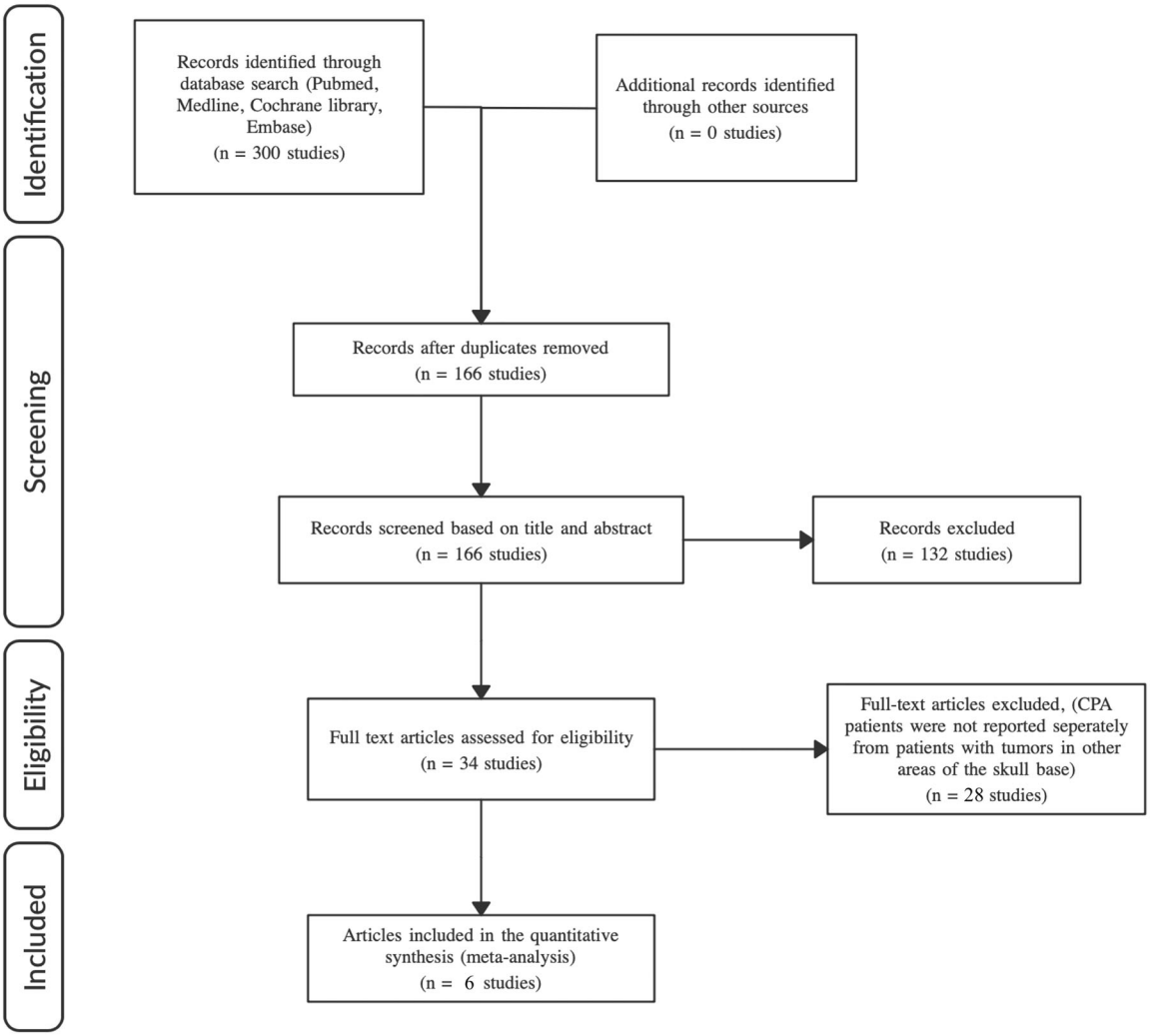

Figure 1. PRISMA diagram of the systematic review and meta-analysis of the included studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

search term: ('radiosurgery' or 'cyber knife' or 'gamma knife' or 'linac') and 'meningioma' and ('cerebellopontine' or 'IAC' or 'internal auditory canal' or 'internal auditory meatus' or 'petrous'). The search was performed under 'all fields' for all databases. Articles found with this search were reviewed according to the study's selection criteria and the Cochrane systemic reviewing standards.[18] References of these qualifying articles were also screened for potential inclusion.

Selection criteria

Articles were selected if they met the following inclusion criteria: (1) the article described patients that underwent treatment of CPA meningiomas by SRS, (2) the article clearly defined the patient population undergoing SRS of CPA meningiomas and clearly differentiated them from patients undergoing treatment of tumors in other areas of the skull base, (3) the article reported one of the following measures: tumor control, trigeminal nerve deterioration, facial nerve deterioration, hearing loss, diplopia, hydrocephalus and AREs. Editorials, conference papers, letters to the editor, abstracts, presentations, literature reviews, studies involving pediatric patients and studies with < 3 patients were excluded from this study. Only papers that were written in the English language were included. Studies including patients with petroclival meningiomas were excluded due to the more challenging nature and higher morbidity of these deep-seated tumors, in addition their complications have previously been characterized in the literature.[19] In addition, foramen magnum tumors were excluded as their location is more caudal and often presents with a completely separate constellation of symptoms for meningiomas of the CPA such as headache, numbness, ataxia, neck pain with sometimes minimal cranial nerve deficits.[20] The authors used Covidence (Melbourne, Australia) for systematic review management software for review organization. Articles from the initial search were screened by two authors (JG, KS) for their suitability for inclusion; any disagreements were resolved by consensus among all of the authors of the study.

Data extraction

Data was collected from the text, tables, graphs and supplementary material provided in the articles by the same authors who performed the screening. From the studies selected for inclusion, the extracted data included patient demographic characteristics (number of patients, age, gender), length of follow-up, tumor volume, previous resection attempts, tumor extension into the IAC, radiosurgical characteristics (SRS method, marginal dose, maximal dose, number of isocenters, isodose line) in addition to

Table 1. Study characteristics from the 6 studies of SRS treatment for CPA meningiomas included in this Meta-analysis.

Study	N-value	Country	Median (mean) Follow-Up (Months)	Median (mean) Age (Years)	Male/Female	NOS Rating
Ding et al.[13]	177	USA	(47.4) radiological, (45.8) clinical	(59)	28/149	6
El-Shehaby et al.[10]	66	Egypt	42	(50)	17/ 49	6
Jahanbakhshi et al.[14]	93	Iran	24	(52.2)	18/75	6
Kim et al.[11]	50	South Korea	48	(55.8)	5/45	6
Pollock et al.[12]	16	USA	36	63	1/15	6
Chang et al.[28]	4	Taiwan	90	55	0/4	5

the postprocedure variables mentioned previously. Symptomatic deterioration was classified as having a worsening of preprocedure function or a total loss of cranial nerve function postprocedural. Trigeminal neuropathy was characterized as including both facial sensation deficits in addition to trigeminal pain sensation. In the event of any disagreement with decisions of data extraction, the decision was made by consensus among all of the authors. Data was captured and organized on a spreadsheet using Microsoft Excel Version 16.26 (Microsoft Corporation, Redmond, WA) and subsequently stored on the Harvard Dataverse repository for public access (Harvard University, Boston, MA).[21] Each study included in the meta-analysis was thoroughly examined and assessed for the possibility of bias. This process was in accordance to the checklist provided by the Newcastle-Ottawa Scale (NOS) for ensuring retrospective cohort study quality.[22]

Statistical analysis

Quantitative variables were expressed either as median or mean. Individual patient data regarding outcomes of tumor control, hearing loss, facial nerve deterioration, trigeminal symptoms, diplopia, hydrocephalus and ARE data was extracted specifically from each patient. This data was aggregated into groups of either $\leq$ 13 Gy median marginal dose or $>$ 13 Gy marginal dose; $\geq$ 26 Gy median maximal dose or $<$ 26 Gy maximal dose; and $\geq$ 6 cm^3 median tumor volume or $<$ 6 cm^3 tumor volume based off of their studies' median values for the purpose of statistical testing. Statistical analysis and forest plot production was performed on *Review Manager (RevMan)* [Computer program] (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Statistical risk ratio was calculating using methods previously described in published literature with an α level of 0.05 to determine statistical significance.[23] A random effects model was applied to statistical testing if the I^2 $>$ greater than 50%; otherwise the fixed effects method was used.

Publication bias

Detection of publication bias was attempted using funnel plots of each variable created by the *Review Manager (RevMan)* software. Funnel plots were assessed for any asymmetry that could potentially indicate the present of publication bias. This was performed by methods previously established for detecting publication bias.[24]

Results

Literature search

The database search yielded a total of 89 results from PubMed, 86 results from Medline, 124 from Embase and 1 from the Cochrane Library of Systemic Reviews for a total of 300 studies. After removing 134 duplicate studies, 166 articles were screened for eligibility. Screening of the titles and abstracts revealed 34 articles, which were assessed for inclusion in the meta-analysis by full text screening. After applying exclusion criteria, 10 total studies were remained. Two studies provided data of patients from the same institution, and the smaller study was therefore removed.[12,15] In addition, 1 multicenter review included institutions from other studies and the 3 smaller studies were removed due to concern for duplication.[25–27] After removing these 4 studies that potentially involved duplicate data on patients, 6 studies remained.

Reviewing the bibliography of the 6 selected studies yielded no additional articles to be included. The PRISMA flow diagram is displayed in Figure 1. Each study was thoroughly screened for quality according to the NOS criteria.[22] Out of the total possible score of 9, all 6 studies received a 6. All of the included studies lost one point for item S2, as no study described a control group of patients not undergoing SRS. In addition, all of the included studies also lost 2 points for comparability since no study controlled for confounding factors in their measurement of outcomes for tumor control and neurological prognosis.

Demographics

The final meta-analysis included a total of 406 patients undergoing SRS for meningiomas of the CPA. All included studies were retrospective. Three studies[10,13,14] included patients that underwent previous attempts at surgical resection. Of the studies that included patients with previous attempts at resection, the data of these individuals was not separated from patients undergoing primary surgery. Thus, rates of complications were unable to be described for patients undergoing SRS as a primary treatment option from patients undergoing SRS as an adjuvant treatment option. Patient demographics including sample size, gender, mean age, follow-up and description of the SRS hardware for each study is provided in Table 1.

Tumor characteristics

In studies where mean/median tumor volumes were published, this data ranged from 3.6–7.1 cm^3 ($N = 5$ studies). The number of patients with prior surgical resection in each series ranged from ranged from $0 - 100\%$ ($N = 6$ studies). Data on extension of tumors into the IAC were also provided by 4 studies[10–12,14] and ranged from 0–32.3% of patients having IAC extension. Tumor characteristics of individual studies are displayed in Table 2.

Radiosurgical characteristics

Radiosurgery was performed using the Leksell Gamma Knife Models U, B, C or 4C by Elekta (Stockholm, Sweden). Mean/median marginal doses ranged from 12–15 Gy ($N = 6$ studies). Mean/median maximal doses had more variability and ranged

Table 2. Tumor characteristics from the 6 studies of SRS treatment for CPA meningiomas included in this Meta-analysis.

Study	Median (mean) Tumor Volume (cm^3)	Prior Surgical Resection (%)	IAC Involvement (%)
Ding et al.[13]	3.6	30	NA
El-Shehaby et al.[10]	7.1	9	67
Jahanbakhshi et al.[14]	6.0	32.2	0
Kim et al.[11]	(6.1)	0	100
Pollock et al.[12]	5.1	0	100
Chang et al.[28]	NA	0	NA

SRS: stereotactic radiosurgery; CPA: cerebellopontine angle; IAC: internal acoustic canal.

Table 3. Procedural descriptions from the 6 studies of SRS treatment for CPA meningiomas included in this Meta-analysis.

Study	SRS Type	Median (mean) Maximal Dose (Gy)	Median (mean) Isodose (%)	Median (mean) Prescription Dose (Gy)	Median Number of Isocenters
Ding et al.[13]	Gamma Knife	26	50	13	9
El-Shehaby et al.[10]	Gamma Knife Models B,C or U	24	50	12	NA
Jahanbakhshi et al.[14]	Gamma Knife Model B or C	20	65	13.5	13
Kim et al.[11]	Gamma Knife Models U, B, C, 4C, Perfexion, or Icon	(26.3)	(50)	(13.1)	NA
Pollock et al.[12]	Gamma Knife Model C	30	NA	15	11
Chang et al.[28]	Gamma Knife	NA	NA	13.2	NA

SRS: Stereotactic Radiosurgery; CPA: cerebellopontine angle.

from 20–30 Gy ($N = 5$ studies). Mean/median isodose and isocenters ranged from 50–65% ($N = 4$ studies) and 9–13 ($N = 3$ studies). Radiosurgical characteristics for individual studies are displayed in Table 3.

Radiological outcomes

Radiological mean/median follow-up ranged from 24–90 months across all studies. Overall pooled tumor control rate was 95.6% among all 6 studies reporting tumor progression. Tumor control was not associated with increased maximal dose, prescription dose or tumor volume.

Overall rate of tumor regression on postprocedure imaging was 43.8%. There was a higher likelihood of tumor regression on postoperative imaging in studies with a median prescription dose of $>$ 13 Gy (RR 1.27 [95% CI 1.04–1.56, $p = 0.0225$).

Facial nerve

Overall pooled rate of facial nerve preservation without new or worsening neurological deficit was 97.6% among 4 studies.[12–14,28] Facial nerve deterioration was not associated with differences in maximal dose, prescription dose or tumor volume. Hemifacial spasm was reported in one study.[28] Relief of hemifacial spasm was found in 4/6 patients (67%).

Trigeminal nerve

Trigeminal nerve sensation loss data was provided by 4 studies.[12–14,28] Mean rate of sensation preservation was 96.0%. Trigeminal nerve sensation was not associated with differences in maximal dose, prescription dose or tumor volume. Data on trigeminal nerve pain specifically was provided by 2 studies.[12,28] Trigeminal nerve pain improved in 15.8% of patients post procedure.

Hearing loss

Symptoms were reported in 6 studies[10–14,28] and there was a 94.1% hearing preservation rate overall. Incidence of hearing loss was not associated with differences in maximal dose, prescription dose or tumor volume. When comparing the only study reporting that all patients had IAC extension[11] to a study where no patients had IAC extension[14] the difference in patients developing hearing loss was minimal (6% vs 4.3% respectively).

Diplopia

Overall pooled rate of periprocedure diplopia was 2.6% among 3 studies.[12,14,28] Incidence of diplopia was not associated with differences in maximal dose, prescription dose or tumor volume.

Adverse radiation effects

Rates of AREs were reported in 3 studies.[10,13,14] Pooled symptomatic AREs were 0.6% which included patients suffering from headache, ataxia and facial weakness from 10–11 months post-SRS. Asymptomatic effects were found in 0.6% of patients and were characterized by peri-tumoral hyperintensity and edema on imaging with neurological deficits. Total AREs including both symptomatic and asymptomatic were found in 3.9%. There were no statistically significant difference of adverse radiation effects associated with maximal dose, prescription dose and tumor volume.

Hydrocephalus

Overall pooled rate of periprocedural hydrocephalus was 2.0% across 3 studies.[13,14,28] Postprocedural hydrocephalus was not associated with differences in maximal dose, prescription dose or tumor volume.

Publication bias

During the literature search no authors encountered any evidence of data that had not been reported in full or previously published. However, it admittingly is hard to detect unpublished data unless it is specifically affiliated with a home institution or group. Calculation of funnel plots for each variable revealed no obvious asymmetry that would indicate possible publication bias; however this is somewhat limited due to the nature of the variables having < 4 studies reporting.

Discussion

Tumor control

Previously published literature has provided evidence that higher prescription dosages result in an increased overall increased rate of tumor control for various intracranial lesions to include vestibular schwannoma, craniopharyngioma, chordoma and meningioma.[29–34] Tumor control was not increased in studies with higher prescriptions doses in this meta-analysis to any statistical significance, however tumor regression postprocedure was associated with studies including median prescription doses of $>$ 13 Gy. Therefore, high prescription doses likely could lead to increased tumor regression, however no differences were found in tumor control as a result of the lower relative power of this meta-analysis when compared to other more common intracranial pathologies.

Overall, the aggregate tumor control rate was 95.6%, which is similar to tumor control rates of meningiomas found in other areas of the skull base treated with SRS of comparable size.[35] When reviewing the literature for SRS treatment of the higher grade atypical and anaplastic meningiomas only, 1 study reporting patients undergoing SRS for recurrent and incompletely resected meningiomas had a tumor control rate of 70% at 5 years. Their median treated tumor volume was 4.8 ml while using a marginal dosage of 14 Gy.[36] Additionally, another study of 127 treated lesions of atypical and anaplastic meningiomas had an overall tumor control rate of 67% at 5 years. They used a median marginal dose of 16 Gy and included tumors with a mean volume of 1.71 ml.[37] Unfortunately, aggregated data for specific tumor grades could not be calculated in this meta-analysis, as specific outcomes were not stratified by tumor grades in any of the included studies.

Cranial nerve outcomes

Interestingly, higher rates of radiation doses did not increase the risk of hearing loss in this meta-analysis. Higher rates of radiation dosing have been reported to increase hearing loss when treating patient with vestibular schwannoma of CPA.[38–41] These studies largely concluded that increased rates of hearing loss occur with higher prescription dosages, and it is proposed that a maximum threshold cochlear dose of 5 Gy would lead to improved hearing for patients postprocedure. A recent study conducted by Carlstrom et al was a comparative trial of SRS for CPA meningiomas and vestibular schwannoma. It was initially reviewed in this review but excluded due to its potential for duplication of patient data with another study.[15] They found that the threshold cochlear dose of 5 Gy established as a dosimetric parameter for vestibular schwannoma treatment may not be applicable other pathologies of the CPA such as meningioma, and they propose that these dosimetric parameters may be specific to each pathology.[42–44] Therefore, a maximum cochlear dose for meningioma should be sought to optimize outcomes post-SRS for this patient population for the purposes of achieving optimal tumor control and minimizing complications.

When considering other variables that could potentially affect postprocedural hearing outcome, IAC extension appeared to not cause a significant difference in postprocedural hearing outcome. While only one study reported that all meningiomas had extension into the IAC,[11] another single study reported that no patient had meningioma extension into the IAC.[14] Interestingly, the difference in patients developing hearing loss was minimal and not statistically significant (6% vs 4.3% respectively, $N = 143$).

In a large meta-analysis by Yang et al of 2,204 total patients, they found that facial nerve preservation was more successful when vestibular schwannomas were treated with a marginal dose $<$ 13 Gy.[16] This variable did not achieve statistical significance in this analysis for meningioma. One explanation could be that this analysis was not sufficiently powered enough to make this conclusion ($N = 282$ vs $N = 2{,}204$) due to the much lower prevalence of CPA meningiomas when compared to vestibular schwannoma. Another explanation could be that dosimetric thresholds for improving postprocedural cranial nerve functions are specific for each pathology and have yet to be elucidated for meningiomas of the CPA.

Overall trigeminal nerve deterioration was 4.0% in this analysis, and predictors of post-SRS deterioration were not clear for this outcome. There is evidence that trigeminal neuropathy post-radiosurgery is not related to tumor volume, radiation dosing, volume of the fifth cranial nerve or to the proportionality of the fifth cranial nerve that is cisternal when considering vestibular schwannoma of the CPA, which was measured in a retrospective study of 179 patients.[45] In this meta-analysis, tumor volume, prescription dose and maximal dose were not associated with trigeminal neuropathy outcomes to any statistical significance. It is interesting that there is a relatively lower number of studies reporting this outcome when compared to the other cranial nerves, however trigeminal symptoms appear to be a widely prevalent preprocedural symptom in patients with CPA meningioma.[6,38,46]

Adverse radiation effects

In previously published literature, increases in radiation dosing have been reported to increase incidence of AREs when patients undergo radiosurgery.[47,48] This could potentially be alleviated in some patients by a method recently proposed whereby staged-volume radiosurgery is used to allow patients to undergo shorter amounts of radiosurgery at one time, and often with higher dosages. This allows the treatment team to remove larger, more aggressive, tumors in patients while reducing the rate of permanent AREs.[49] Stojadinovic et al reported that radiation toxicity was more likely to occur in tumors with smaller surface areas.[50,51] It is postulated that lower tumor surface areas allow for more spilled dosing of radiation to damage the surrounding structures and neural tissue, and thus more AREs occur postprocedure. This meta-analysis did not find any statistically significant associations with AREs and dose or tumor volume.

Overall, the 6% rate of AREs for CPA meningioma found in this meta-analysis is largely comparable to the rates of AREs for arteriovenous malformations, but it seems to be a lower rate than of AREs found after vestibular schwannoma treatment when using similar prescription dosages.[46,47,52,53]

Limitations

Due to the uncommon nature of this disease, and also the particular modality of treatment which was the focus of this study, the total number of patients for meta-analysis was small. This reduces the overall power of the study, making it hard to find statistically significant associations.

One limitation of this meta-analysis is the retrospective and observational nature of all included studies. No included study offered adequate case-controls or randomized clinical trials in their methodology. Therefore, there was no way to control for standardization among the treated patients, varied follow-up periods, tumor control definitions, and surgical outcome definitions.

In addition, data of patients undergoing SRS with an increased length of follow-up were largely limited. Only two studies in this systematic review had an average length of follow-up spanning $>$ 5 years. These two studies also included only 10 patients when considered together. Therefore, it is difficult to make conclusions on the effectiveness of tumor control long-term with this data.

Data of patients who underwent previous attempts at resection with microsurgery were not separated from patients who underwent SRS as the initial treatment modality in the included studies. Therefore, there was no way to accurately report rates of postprocedure complications and tumor control separately for these two patient populations.

Finally, another limitation was the lack of a histological grading for the tumors among the studies. World Health Organization grade II or III meningiomas typically have poorer surgical and radiological outcomes when compared to the more common grade I meningiomas.[54,55] The included studies did not offer data that was stratified by tumor grade, and therefore no aggregated data or conclusions could be made for the different tumor grade as well. Future studies should consider providing stratified data by tumor grade to offer the most utility out of their data.

Conclusions

This systematic review and meta-analysis concludes SRS treatment for meningiomas of the CPA is an effective modality offering excellent rates of tumor control within 5 years postprocedure while also allowing for minimal morbidity. There is evidence to suggest that higher prescription doses may lead to increased tumor regression after the procedure. Neurosurgeons should consider this data when with patient discussions and deciding on optimal treatment modalities.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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