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ORIGINAL ARTICLE - TUMOR - MENINGIOMA

Stereotactic radiosurgery for clinoid meningiomas: a multi-institutional study

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Abstract

Purpose Resection of clinoid meningiomas can be associated with significant morbidity. Experience with stereotactic radiosurgery (SRS) for clinoid meningiomas remains limited. We studied the safety and effectiveness of SRS for clinoid meningiomas.

Methods From twelve institutions participating in the International Radiosurgery Research Foundation, we pooled patients treated with SRS for radiologically suspected or histologically confirmed WHO grade I clinoid meningiomas.

Results Two hundred seven patients (median age: 56 years) underwent SRS for clinoid meningiomas. Median treatment volume was 8.02 cm^3, and 87% of tumors were immediately adjacent to the optic apparatus. The median tumor prescription dose was 12 Gy, and the median maximal dose to the anterior optic apparatus was 8.5 Gy. During a median post-SRS imaging follow-up of 51.1 months, 7% of patients experienced tumor progression. Greater margin SRS dose (HR = 0.700, $p = 0.007$) and pre-SRS radiotherapy (HR = 0.004, $p < 0.001$) were independent predictors of better tumor control. During median visual follow-up of 48 months, visual function declined in 8% of patients. Pre-SRS visual deficit (HR = 2.938, $p = 0.048$) and maximal radiation dose to the optic apparatus of ≥ 10 Gy (HR = 11.297, $p = 0.02$) independently predicted greater risk of post-SRS visual decline. Four patients experienced new post-SRS cranial nerve V neuropathy.

Conclusions SRS allows durable control of clinoid meningiomas and visual preservation in the majority of patients. Greater radiosurgical prescription dose is associated with better tumor control. Radiation dose to the optic apparatus of ≥ 10 Gy and visual impairment before the SRS increase risk of visual deterioration.

Keywords Stereotactic radiosurgery · Meningioma · Local control · Visual outcomes

Introduction

Meningiomas are the most common primary intracranial neoplasms comprising approximately one-third of all primary CNS tumors [9, 43]. Clinoid meningiomas comprise less than 10% of supratentorial meningiomas [4]. Microsurgical resection is the treatment of choice of clinoid meningiomas and can be curative [4, 16, 29]. However, close proximity and/or encasement of the internal carotid artery and invasion of the optic canal and cavernous sinus can limit the extent of resection of clinoid meningiomas and increase the risk of post-operative morbidity [3, 21, 21, 24, 29, 39, 44]. Surgical resection of clinoid meningiomas can be associated with significant post-operative morbidity and mortality as compared to other intracranial and skull base meningiomas of other locations [3, 4, 16]. Stereotactic radiosurgery (SRS) is an established adjuvant and up-front treatment modality for atypical and malignant meningiomas, after incomplete tumor resection and at time

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of disease recurrence/progression [5, 7, 19, 34, 42]. SRS is also increasingly used for the up-front treatment of skull base meningiomas, especially for patients unfit for open surgery, and it was shown to afford durable tumor control with a low risk of morbidity [1, 5, 14, 30, 31, 37, 38]. However, the majority of previously published SRS series of skull base meningiomas did not specifically consider outcomes of clinoid meningiomas. A recent single-institution series of 61 patients treated with SRS for anterior clinoid meningiomas reported that during a median post-SRS follow-up of 75 months, all patients achieved tumor control without new neurological deficits [2]. However, larger studies are warranted to better understand and establish the safety and effectiveness of SRS for this challenging disease.

In this large multicenter series, we investigated the safety and effectiveness of SRS for clinoid meningiomas.

Methods

Patients

Patients treated with the SRS for WHO grade I clinoid meningioma were identified from institutions affiliated with the International Radiosurgery Research Foundation (protocol R-16–10). Signed informed consent was not required. The diagnosis of meningiomas was based on MRI or histological examination (when available). Patients diagnosed with WHO grade II or III meningiomas were excluded. De-identified patient data was pooled for analyses. Data collection was approved by institutional review boards at each of the participating centers.

Clinical assessment

We gathered information about patient gender, age at meningioma diagnosis, presenting symptoms, pre-SRS functional status and ophthalmological function, history and extent of resection, history of fractionated radiation therapy, and interval between resection and SRS. Information about the WHO grade of the resected meningioma was obtained when available.

Stereotactic radiosurgery technique

SRS was performed following standard techniques using Gamma Knife units (Elekta AB, Stockholm, Sweden) depending on technology availability at participating centers. The decision to use single-fraction or hypofractionated SRS techniques was made at the discretion of the treating team. SRS planning was performed by a multidisciplinary team and was tailored to patient needs. Margin and maximum tumor doses, dose to the optic apparatus (ipsilateral optic nerve, chiasm, and tracts), treatment volume (cm^3), the number of isocenters, and the number of fractions, were recorded.

Clinical and radiographic follow-up

Imaging and clinical follow-up were typically done at 3- to 6-months intervals for the first 2 years after SRS and annually thereafter. Tumor volume on post-SRS studies was compared to respective pre-SRS studies. Meningioma volume at each follow-up visit was categorized as stable (volumetric changes $< 20\%$), regression (decrease by $\geq 20\%$), or progression (increase by $\geq 20\%$) [8, 45]. Time from SRS to the volume change of the meningioma was recorded. Other post-SRS treatments and time and cause of death were recorded.

Visual follow-up was obtained through a combination of ophthalmic visual field examination and outpatient clinic visits. Visual field testing was performed as clinically indicated and/or according to the protocol of the individual sites. Visual status change at the last follow-up visit as compared to pre-SRS visual function was categorized by the treating team as not changed, improved, or declined.

We also recorded presence, type and timing of any new neurological deficits, or other SRS-related complications according to the RTOG CNS toxicity criteria [33].

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). $P < 0.05$ was considered statistically significant. Progression-free survival (PFS) was defined as the interval from SRS to last imaging follow-up or radiographic tumor progression, whichever occurred first. Time to visual decline was defined as the interval from SRS to deterioration of visual function (as deemed by the treating team) either by formal ophthalmologic examination or clinical examination or last follow-up. Patients who did not achieve an index event were censored at the last follow-up. The association of clinical and SRS factors with PFS and time to visual change was investigated using the Kaplan–Meier method and univariate and multivariate Cox regression analyses, with predictors in univariate analyses reaching p value of < 0.1 entered in multivariate Cox regression models. Results of the Cox regression analysis are presented as hazard ratio (HR), 95% confidence interval (95% CI), and p value.

Results

Two hundred seven patients who underwent SRS for histologically confirmed or radiologically suspected WHO grade I clinoid meningioma were studied (Table 1). The

Table 1 Baseline characteristics ($n = 207$)

Characteristic	*n* (%)
Gender, *n* (%)	
Men	45 (22%)
Women	162 (78%)
Age (years)	
Median [range]; mean ± SD	56 [24–80]; 54.92 ± 12.53
Karnofsky Performance Index before SRS (score)	
Median [range]; mean ± SD	90 [50–100]; 84.87 ± 12.53
Available data	115 (56%)
Pre-SRS visual deficit, *n* (%)	
Yes	100 (48%)
No	107 (52%)
Other presenting symptoms, *n*[A]	
Headache	42 (20%)
Diplopia	43 (21%)
Ptosis	25 (12%)
Incidental	21 (10%)
Seizure	6 (3%)
Other	35 (17%)
Duration of symptoms (months)	
Median [range]; mean ± SD	9 [0–216]; 17.93 ± 25.52
Available data	181 (87%)
Nearest distance to the optic apparatus (mm)	
Median [range]; mean ± SD	0 [0–2.1]; 0.38 ± 3.41
In direct contact with optic pathway	181 (87%)
Other meningiomas, *n* (%)	26 (13%)
Index meningioma surgery before SRS, *n* (%)	57 (28%)
Number of prior resections, *n* (%)	
One	42 (20%)
Two	13 (6%)
Three or more	2 (1%)
Extent of resection	
Gross total resection	10 (5%)
Subtotal resection	41 (20%)
Biopsy	4 (2%)
Interval between surgery and SRS (months)	
Median [range]; mean ± SD	9 [1–183]; 33.20 ± 46.05
Pre-SRS fractionated radiation therapy, *n* (%)	2 (1%)

[A]Total percentage is greater than 100% because some patients had more than one presenting symptom

SD, standard deviation

majority of patients were women (78%). The median age of the study patients was 56 years. Forty-eight percent of patients had visual deficits before the SRS. The nearest distance between meningioma and anterior optic apparatus ranged from 0 to 2.1 mm, and 87% of tumors were in direct contact with the optic apparatus. Fifty-seven (28%) patients had histories of at least one resection surgery of the clinoid meningioma. Two (1%) patients also had histories of fractionated radiation therapy of an index lesion before SRS.

SRS characteristics

Radiosurgical procedural characteristics are presented in Table 2. The majority of patients were treated using single-fraction SRS (92.8%). Median treatment volume and prescription dose were 8.02 cm^3 (range: 0.13–50.86 cm^3) and 12 Gy (range: 7–25 Gy), respectively. The median maximal dose to any portion of the anterior optic apparatus was 8.5 Gy (range: 3–16 Gy). Median maximal doses to the optic nerve, optic chiasm, and optic tract were 8.20 Gy, 7.55 Gy,

Table 2 Treatment characteristics

Parameters	
Number of SRS fractions	
Single	192 (92.8%)
Two	1 (0.5%)
Three	1 (0.5%)
Four	9 (4.3%)
Five	4 (1.9%)
Treatment volume (cm^3)	
Median [range]; mean ± SD	8.02 [0.13–50.86]; 9.56 ± 7.60
Number of isocenters	
Median [range]; mean ± SD	16 [1–48]; 18.75 ± 10.50
Margin tumor dose (Gy)	
Median [range]; mean ± SD	12 [7–25]; 13.00 ± 2.53
Biologically effective dose (Gy)	
Median [range]; mean ± SD	60 [23.3–101.3]; 63.56 ± 12.99
Maximal tumor dose (Gy)	
Median [range]; mean ± SD	24 [8–50]; 24.30 ± 4.94
Maximal dose to optic apparatus	
Median [range]; mean ± SD	8.50 [3–16]; 8.64 ± 2.01
Maximal dose to the optic nerve (Gy)	
Median [range]; mean ± SD	8.20 [2–15]; 8.23 ± 1.99
Maximal dose to optic chiasm (Gy)	
Median [range]; mean ± SD	7.55 [0–16]; 7.31 ± 2.24
Maximal dose to optic tract (Gy)	
Median [range]; mean ± SD	5.90 [0–12]; 5.68 ± 2.02

SD, standard deviation

and 5.90 Gy, respectively. Fifteen patients underwent hypofractionated SRS with the number of fractions ranging from two to five. Treatment volume (11.64 ± 15.35 cm^3 vs. 9.41 ± 6.75 cm^3, $p = 0.289$) and distance to nearest distance to the optic apparatus (0.49 ± 0.75 cm vs. 1.34 ± 3.33, p = 0.327) were not significantly different in patients treated with hypofractionated vs. single-fraction SRS.

Tumor control

During median post-SRS imaging follow-up of 51.1 months (range: 6–239 months), the majority of clinoid meningiomas treated with SRS remained stable (51%) or regressed (42%) (Table 3). Fourteen patients (7%) experienced tumor progression at a median time interval from SRS to tumor progression of 111 months (range: 12–233 months). Fourteen patients underwent resection or repeated SRS after an index SRS.

In univariate Cox regression analysis, larger margin SRS dose ($p = 0.021$), smaller tumor volume ($p = 0.029$), and pre-SRS radiotherapy ($p = 0.001$) were associated with better tumor control (Table 4). In multivariate Cox regression models, larger margin SRS dose (HR = 0.700 95%CI [0.540–0.907] $p = 0.007$) and pre-SRS radiotherapy (HR = 0.004 95%CI [< 0.001–0.083] $p < 0.001$) remained as independent predictors of better tumor control.

Visual outcomes

At least one post-SRS visual follow-up was available for 182 (88%) patients with a median visual follow-up of 48 months (range: 0.2–233.34 months) (Table 3). Visual function remained stable in the majority of patients (76%) and improved in 29 (16%) patients. Visual function decline was documented in 14 (8%) patients at a median time interval of 41 months (range: 1–123 months) after the SRS of which 3 patients (21%) had tumor progression. The median time from SRS to visual function improvement was 9 months (range: 1–79 months). Visual outcomes were not associated with tumor control ($p = 0.183$).

In Kaplan–Meier analyses, the visual decline was predicted by the presence of a visual deficit before SRS ($p = 0.001$; Fig. 1A) and maximal radiation dose to the optic apparatus of ≥ 10 Gy (vs. < 10 Gy) ($p = 0.044$; Fig. 1B). In univariate Cox regression analysis, greater risk of post-SRS visual decline was associated with the presence of visual deficit before SRS ($p = 0.02$) and maximal radiation dose to the optic apparatus of ≥ 10 Gy (vs. < 10 Gy) ($p = 0.051$) (Table 5). In multivariate Cox regression analysis, greater risk of post-SRS visual decline remained independently associated with the presence of visual deficit before SRS (HR = 2.938 95%CI [1.010–8.546] $p = 0.020$) and maximal radiation dose to the optic apparatus of ≥ 10 Gy (vs. < 10 Gy) (HR = 11.297 95%CI [1.476–86.455] $p = 0.020$).

Other adverse events

During median clinical follow-up of 42 months (range: 0–240 months), four (2%) patients experienced new cranial nerve V neuropathy from 26 to 73 months after SRS. One patient was diagnosed with new hypothyroidism 36 months after the SRS. Other reported adverse events included dizziness ($n = 3$), headache ($n = 2$), and seizures ($n = 2$). Seven (3%) patients died during the observation period from causes unrelated to their meningioma.

Discussion

In this large multi-institutional series, we explored the safety and effectiveness of SRS for clinoid meningiomas which are often a surgically challenging tumor type and location. Treatment with SRS achieved durable control of clinoid meningiomas in the vast majority of patients while conferring a low risk of permanent neurological deficit. A higher prescription radiation dose and pre-SRS radiotherapy were

Table 3 Imaging follow-up

Imaging follow-up	
Imaging follow-up duration (months)	
Median [range]; mean ± SD	51.1 [6.0–239.0]; 63.81 ± 46.64
Imaging outcomes at last follow-up, *n* (%)	
Available data	202 (99%)
Stable	103 (51%)
Regression	85 (42%)
Progression	14 (7%)
Time to progression (months)	
Median [range]; mean ± SD	111.0 [12.0–233.0]; 102.93 ± 65.09
Treatment after index SRS	
Tumor resection	4 (2%)
Repeated SRS	10 (5%)
Visual follow-up	
Available data, *n* (%)	182 (88%)
Follow-up duration (months)	
Median [range]; mean ± SD	48.0 [0.2–233.34]; 59.10 ± 45.86
Outcome at last follow-up, *n* (%)	
Available data	182 (88%)
No change	139 (76%)
Improved	29 (16%)
Declined	14 (8%)
Time to visual decline	
Median [range]; mean ± SD	51.00 [1.0–123.0]; 53.50 ± 40.36
Time to visual improvement	
Median [range]; mean ± SD	9.0 [1.0–79.0]; 17.03 ± 19.15

SD, standard deviation

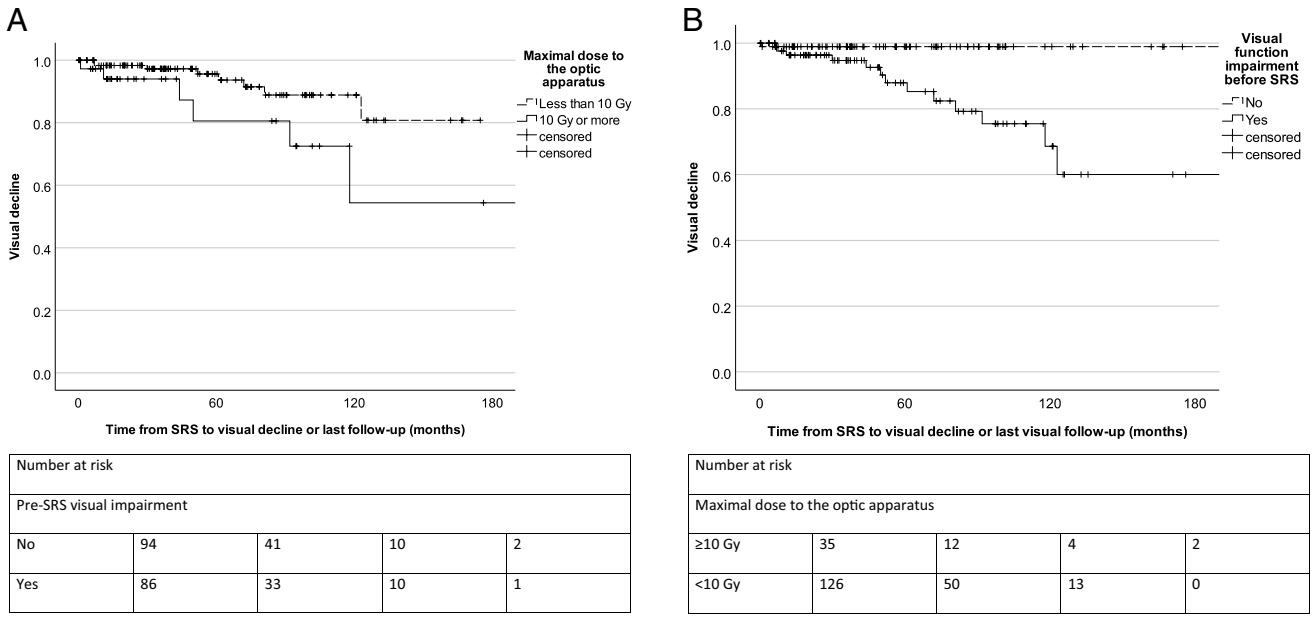
Table 4 Cox regression analysis of predictors of progression of SRS-treated clinoid meningiomas; hazards ratio [95% confidence interval], *p*-value

	Univariate	Multivariate
Gender	0.669 [1.78–2.513] 0.551	-
Age	1.022 [.979–1.068] 0.322	-
Margin dose (Gy)	**0.744 [0.579–0.956] 0.021**	**0.700 [0.540–0.907] 0.007**
Tumor volume at SRS (cm^3)	**1.058 [1.006–1.113] 0.029**	$P = 0.341$
Pre-SRS surgery[A]	1.259 [0.385–4.114] 0.703	-
Pre-SRS fractionated radiotherapy[A]	**0.011 [0.001–0.174] 0.001**	**0.004 [< 0.001–0.083] < 0.001**
Interval between surgery and SRS	0.923 (0.758–1.123) 0.422	-
Duration of symptoms (months)	1.009 (0.992–1.025) 0.293	-

[A] 1 = yes, 0 = no

independently associated with better local control of clinoid meningiomas. Visual function remained stable or improved in the majority of our patients. Maximal radiation dose to the anterior optic apparatus of ≥ 10 Gy and visual impairment before SRS emerged predicted post-SRS visual function.

During a median post-SRS follow-up of 51 months, 41% of meningiomas regressed and only 7% of patients experienced radiological progression from 12 to 233 months after the SRS. In recent series of 61 patients treated with GKRS for anterior clinoid meningiomas, Akyoldas with colleagues reported a tumor control rate of 100% during a median radiographic follow-up of 75 months (range: 27–126 months) [2]. Demiral with colleagues reported local tumor control at 3 years of 89% in a series of 22 patients treated with hypofractionated stereotactic radiotherapy (25 Gy delivered in 5 fractions) for anterior clinoid meningiomas [12]. Numerous authors have documented durable local control of skull base meningiomas that typically exceeds 90%. However, clinoid meningioma patients were typically considered together with meningiomas residing in other anatomical locations [1, 5,



Number at risk				
Pre-SRS visual impairment				
No	94	41	10	2
Yes	86	33	10	1

Number at risk				
Maximal dose to the optic apparatus				
≥10 Gy	35	12	4	2
<10 Gy	126	50	13	0

Fig. 1 Kaplan–Meier curve of visual decline stratified by visual deficit before SRS (panel **A**; yes vs. no, $p=0.001$) and maximal dose to the optic apparatus (panel **B**; ≥ 10 Gy vs. < 10 Gy; $p=0.044$)

Table 5 Predictors of visual decline; hazards ratio [95% confidence interval], *p*-value

	Univariate	Multivariate
Gender	2.145 (0.564–8.154) 0.263	-
Age	1.008 (0.963–1.056) 0.723	-
Margin dose (Gy)	1.021 (0.760–1.373) 0.889	-
Tumor volume at SRS (cm^3)	1.025 (0.972–1.080) 0.361	-
Maximal dose to the optic apparatus	1.123 (0.871–1.448) 0.369	-
Maximal dose to the optic apparatus ≥ 10 Gy	**2.887 (0.995–8.376) 0.051**	**11.297 (1.476–86.455) 0.020**
Visual deficit before SRS	**11.218 (1.465–85.870) 0.02**	**2.938 (1.010–8.546) 0.048**
Tumor in contact with the optic apparatus	1.076 (0.557–2.078) 0.827	-
Tumor progression (imaging)	2.612 (0.694–9.828) 0.156	-
Tumor margin dose (Gy)	1.021 (0.760–1.373) 0.889	-
Pre-SRS surgery	0.597 (0.199–1.789) 0.356	-
Pre-SRS fractionated radiotherapy	$P=1.00$	-
Duration of symptoms (months)	1.014 (0.997–1.033) 0.110	-
Interval between surgery and SRS	1.003 (0.970–1.037) 0.882	-

14, 30, 37, 38]. A large multicentered study that analyzed results of 3768 meningiomas treated with SRS reported 5-year and 10-year progression-free survival rates of 95% and 89%, with better local control of skull base meningiomas when compared to convexity meningiomas [32]. Our study provides the largest sample size of clinoid meningiomas treated with SRS suggesting that SRS affords durable local control and, therefore, should be considered for management for this challenging disease.

Higher margin radiation dose was an independent predictor of superior local control of clinoid meningiomas. These findings are consistent with prior studies documenting the importance of adequate radiation dose required for optimized local control of intracranial meningiomas [15, 25, 41]. In our series, the median prescription dose for clinoid meningiomas was 12 Gy, which corresponds to a previous SRS series of clinoid meningiomas [2], and it is within the range of radiosurgical dose from 12 to 16 Gy that is typically recommended for WHO grade I meningiomas [10, 13, 22, 35]. There remains a possibility, however, that some of our patients harbored other tumor types or higher WHO grade meningiomas because the histological diagnosis was not available for 72% of patients. Nevertheless, our results indicate a prescription radiation dose of at least 12 Gy is

required for tumors that are most consistent with clinoid meningiomas in order to maximize long-term disease control.

Seven percent of our patients were selected for hypofractionated (2–5 fractions) SRS. Hypofractionated SRS integrates spatial conformity of SRS with tissue repair between fractions and has been shown to allow excellent tumor control with a good safety profile for meningiomas residing in close proximity to critical structures, such as the optic apparatus [1, 5, 11]. Hypofractionated SRS is considered for clinoid meningiomas abutting optic structures and/or large tumors to optimize the preservation of neurological function. While the tolerance of the anterior optic pathways is often defined within a range of 8 to 12 Gy in a single fraction, the maximum dose tolerance to these same structures has been suggested as 25 Gy in 5 fractions [18].

Visual function remained stable (76%) or improved (16%) in the majority of patients. Visual preservation rate in the present series was similar to visual outcomes of perioptic meningiomas (typically located within 3 mm of the anterior optic apparatus) treated with single-session or multi-session SRS [1, 5, 23]. Akyoldas with colleagues reported that visual function improved (55%) or remained stable (45%) in all patients treated with SRS for anterior clinoid process meningioma [2]. In surgical series of clinoid meningiomas, the pooled incidence rate of visual function improvement was 48% [16]. However, variability of reported rates of visual function outcomes after resection of clinoid meningiomas was high [16] with reported rates of visual improvement across series ranging from ≤ 25% [17, 39] to > 70% [21, 28, 40]. Tumor resection and decompression of the anterior optic apparatus should be considered for all patients presenting with clinoid meningioma causing optic nerve compression and visual function impairment [16, 29]. However, SRS can also allow visual function stability and/or improvement, and SRS should be considered for patients with visual function impairment who are unable or unwilling to undergo resection. In the current series, visual function improved or remained stable in 16% and 76% of patients, respectively.

Post-SRS visual function decline occurred in 8% of our patients at a median interval of 51 months after SRS. Maximal radiation dose to the anterior optic apparatus of 10 Gy or greater and the presence of visual impairment before SRS were independent predictors of post-SRS visual decline, indicating the importance of patient selection and meticulous SRS planning for clinoid meningiomas. Prior studies have demonstrated that irradiation of the optic nerve with doses less than 10 Gy poses a minimal risk for optic neuropathy, with increasing risk of visual complications with radiation doses exceeding 10–12 Gy [5, 20, 26, 36]. A pooled incidence rate of decline in visual function following resection of clinoid meningiomas was reported as 4.5% [16], but individual reports range from 0 [40] to more than 10% [4, 27] noting study variability with regard to patient selection, surgical techniques, and follow-up duration. The risk of other permanent adverse events after SRS for clinoid meningiomas was low. Only 2% of patients developed new cranial nerve V neuropathy. Surgical and radiation therapy approaches should be considered on an individual basis for clinoid meningiomas. Hypofractionated SRS should be considered for tumors that are immediately adjacent to the optic apparatus in order to optimize visual function preservation rates [1, 11].

Study limitations and strengths

The majority of our patients did not have a pathologic diagnosis of WHO grade I meningioma. However, clinical history and contrast-enhanced brain MRI showing avidly enhancing extra-axial tumor are typically sufficient to reliably diagnose meningioma, particularly with serial examinations. We also acknowledge potential differences in technology, treatment devices, and level of experience among the participating centers of this study. Variability within and among treatment centers may affect treatment delivery and outcomes [6]. Most patients were treated in a single-session approach using the Gamma Knife radiosurgery devices; therefore, our results cannot be directly generalized to other radiotherapy techniques. Finally, a central review of imaging was not performed; therefore, a more detailed assessment of meningioma anatomic location was not performed. Despite these limitations, this is, to our knowledge, the largest series of clinoid meningioma patients treated with SRS.

Conclusions

SRS achieves durable local control of clinoid meningiomas with a low risk of permanent neurological deficits. Higher radiation prescription is associated with better local control of clinoid meningiomas. Visual function decline, while rare after SRS for clinoid meningiomas, is associated with maximal dose to the anterior optic apparatus of ≥ 10 Gy and presence of visual impairment prior to SRS. Our findings can be important for treatment decision-making for this surgically challenging tumor type.

Data availability Available upon request.

Code availability N/A.

Declarations

Ethics approval Data collection was approved at each individual center participating in this study.

Consent to participate N/A.

Consent for publication N/A.

Conflict of interest R.L. consultant of Elekta; C.P.C. Carl Zeiss Meditech AG (Speaking Honoraium, unrelated).

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