REVIEW

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Safety and efficacy of single-fraction gamma knife radiosurgery for benign confined cavernous sinus tumors: our experience and literature review

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Abstract

Gamma knife radiosurgery (GKRS) has emerged as a suitable primary treatment option for confined cavernous sinus tumors (CSTs) and residual/recurrent benign tumors extending from the surrounding neighborhood. The aim of this review was to further investigate the safety and efficacy of single-fraction GKRS for primary confined CSTs (hemangioma, meningioma, and schwannoma). This was a retrospective analysis of 16 patients of CSTs, primarily treated with GKRS between 2009 and 2017. The patients underwent follow-up clinical and radiological evaluation at a regular interval. Data on clinical and imaging parameters were analyzed. The published literature on GKRS for CSTs was reviewed. There were total 16 patients (eight meningiomas, seven hemangiomas, and one schwannoma). Patients presented with a headache (56.3%), ptosis (50%), and/or restricted extraocular movements (50%). There was 46.6% tumor volume (TV) reduction after single-fraction GKRS. Hemangiomas showed best TV reduction (64% reduction at > 3-year follow-up) followed by schwannoma (41.5%) and meningioma (25.4%). 56.3% of patients developed transient hypoesthesia in trigeminal nerve distribution. 44.4% of patients became completely pain-free. Among cranial nerves, the superior division of the oculomotor nerve showed best outcome (ptosis 62.5%) followed by an improved range of EOM. There was no adverse event in the form of new-onset deficit, vascular complication, or malignant transformation except for one out of the field failures. Among available treatment options, GKRS is the most suitable option by virtue of its minimally invasive nature, optimal

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long-term tumor control, improvement in cranial neuropathies, mal long-term complications.

Introduction

Complex angioarchitecture, crowded neurovascular neighborhood, scores of geometric triangles, and surgical complexities have made management of cavernous sinus tumors (CSTs) a challenging voyage. Numerous pathologies may involve the cavernous sinus; the most common is meningioma followed by pituitary adenoma, schwannoma, and hemangioma. Surgical complexities and complications have made radiosurgery a suitable alternative, especially for pauci-symptomatic patients [43]. There are no consensus guidelines for management of CSTs, and the recommendations are based on personal experience, institutional practices, and availability of alternate treatment options. A few authors prefer radiosurgery as a primary treatment modality while others as an adjuvant option after downstaging the tumor by surgery. Some are still in favor of conservative management with watchful waiting for confined CSTs [44].

In this study, we have evaluated the treatment outcome after gamma knife radiosurgery (GKRS) for CSTs with special emphasis on lesion control and long-term effect on cranial nerves. The purpose of this analysis is to present the current evidence of efficacy of GKRS for CSTs.

Sex		
Female	14	
Male	2	
Age (Year)		
Mean	42.18	
Range	17-67	
Follow up (month)		
Mean	22.31	
Range	3-96	
Follow up ≥36 month	5	
Follow up >36 month	11	
Tumor Volume (cc)		
Mean	9.16	
Range	2.86-24.80	
Radiological Diagnosis		
CSH	7	
CSM	8	
CSS	1	
Follow up tumor Volume (cc)		
Mean	4.99	
Range	1.14-12.38	
Presenting Symptoms		
Headache	9	
Decreased Vision	2	
3rd Nerve Involvement	9	
4th Nerve Involvement	6	
5th Nerve Involvement	2	
6th Nerve Involvement	12	
Dosimetry Parameters		
Central	Mean (28)	Range (16-48)
Peripheral	Mean (14.3)	Range (8-24)
Reference Isodose	50%	

Fig. 1 Summary of the profile of 16 cavernous sinus tumor patients (CSH cavernous sinus hemangiomas, CSM cavernous sinus meningioma, CSS cavernous sinus schwannoma, GKRS gamma knife radiosurgery)

Material and methods

In this retrospective analysis, we have evaluated the functional outcome and tumor control of benign CSTs in 16 patients (14 female and 2 male, mean age 42 years), treated at our institute using Leksell Gamma Knife model Perfexion (Elekta Instruments, Stockholm, Sweden) from 2009 to 2017. All patients were evaluated on clinical, ophthalmologic, radiological, and radiosurgical parameters. The patients received GKRS as a primary treatment modality on radiologic diagnosis, and in no case, the lesion was ascertained on histologic parameters. The treatment was performed as per the guidelines approved by the institute ethics committee. Only benign confined CSTs (hemangioma, meningioma, and schwannoma) were evaluated in this analysis. All patients either were clinically symptomatic or showed evidence of progressive disease on the serial imaging (Fig. 1). These patients preferred primary GKRS in view of explained risks and minimally invasive nature of the treatment. All available options of management were explained in detail, and pre-treatment consent was obtained from the patient. Follow-up clinical data (16 patients) and radiology (13 patients) were evaluated.

Radiosurgical procedure

Leksell stereotactic G frame (Elekta Instruments) was fixed on the patient's head under local anesthesia. Thin axial MRI cuts of T1-weighted image (T1WI), T2-weighted image (T2WI), and T1 contrast (T1c) were obtained on a 1.5 T MRI machine with the slice thickness of 1 mm/slice. For every patient, two neurosurgeons and one physicist made separate plans, and the best plan on the parameters of coverage, conformity, and selectivity was finalized.

Patients were managed on day care basis. There was no acute complication. All patients were evaluated clinically and radiologically on the regular follow-up interval of every 6 months for the first year and yearly afterward for 3 years. Pre- and post-GKRS clinical and visual evaluation was performed for all the patients. Ten percent change in the tumor volume (TV) was considered significant. Clinical improvement was considered if there was any resolution of neurologic deficit or any relief in the preoperative complaints. Patients with neurological worsening were evaluated if the worsening was a side effect of radiation or tumor progression. All the side

effects were evaluated on Common Terminology Criteria for Adverse Events (CTCAE) v 4.0.

Dosimetry

Tumor volumes (at treatment and follow-up) and radiation dosimetry are presented in Table 1. TV ranged from 2.86 to 24.8 cm^3 (median volume 9.16 cm^3). The lesions were treated with a marginal dose of 13–16 Gy. The mean dose delivered to the tumor center was 28 Gy (16–48 Gy), and that to the periphery was 14.3 Gy (8–24 Gy). Initially, large collimator (8- or 16-mm isocenter) shots were placed in the center of the lesion followed by small (4-mm isocenter) shots towards the periphery of the target to protect surrounding eloquent neurovascular structures (e.g., optic pathway, mesial temporal lobe, and cranial nerves in the lateral wall of the cavernous sinus). A plan was considered better if it had lesser spillage to surrounding areas while maintaining high prescription isodose on the target volume margin. Radiation spillage to visual pathway and brainstem was kept below 8 and 12 Gy, respectively. To prevent the radiation spillage into eloquent structures, beam blocking and/or shielding was used while planning.

Statistical analysis

Descriptive statistics were used to characterize demographic and clinical data. Baseline and post-treatment scores were analyzed by the paired t test and Wilcoxon signed-rank test. Statistical significance was set at p value ≤ 0.05. Data are presented as mean and range for continuous variables and as frequency and percentage for categorical variables. The change in TV was calculated to evaluate the effect of GKRS from the time of treatment to the latest follow-up. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM Corp.).

Literature search

A thorough literature search was performed for CSTs treated with GKRS. PubMed search with keywords radiosurgery, stereotactic, gamma knife, cavernous, hemangioma, meningioma, and schwannoma was performed. All the articles with case series (more than five patients), definite treatment protocol, and adequate follow-up were evaluated. The cross-referenced articles cited in these texts were also checked for literature review. A total of 68 articles were identified, out of which 20 articles (1425 patients) were extensively reviewed. Forty-eight articles were excluded because of insufficient follow-up, less number of patients, and no defined protocol in the study (Fig. 2, Additional Tables 1 and 2).

Results

Demographics

Follow-up neurological evaluation of 16 patients (14 female, 2 male) was obtained at regular intervals (3–96 months). Five patients had more than 36-month follow-up. The tumors included eight cases of meningiomas, seven cases of hemangiomas, and one case of schwannoma. The most common presenting complaints were headache (56.3%), ptosis (50%), and restriction of extraocular movements. No patient presented with seizures. Three patients did not consent for follow-up imaging [two cavernous sinus hemangioma (CSH) and one cavernous sinus meningioma (CSM)].

Clinical outcome

Neurological status improved in 11/16 (68.7%) patients, remained stable in 5/16 (31.3%) patients, and temporarily worsened in 2/16 (12.5%) patients. Nine patients developed new-onset facial hypoesthesia in the distribution of the trigeminal nerve, 3–8 months post GKRS, which improved spontaneously with short-course steroid therapy. Out of 2/16 (12.5%) patients with trigeminal neuralgia, only one reported improvement and reduction in analgesic requirement following GKRS. No patient developed new-onset seizure. Nine out of 16 (56.3%) patients presented with preoperative headache, four out of nine (44.4%) patients became complete pain-free after GKRS while four out of nine (44.4% of patients) showed partial relief, and one patient (11.1%) complained of a persistent headache. The responders show improvement in the headache 8 months (median) after GKRS. Among cranial nerves, the superior division of the oculomotor nerve showed the best clinical improvement with four of eight (50%) patients showing complete relief from ptosis at an 11-month (median) interval. Improvement in other cranial nerves is mentioned in Fig. 3.

Radiological outcome

TV at the time of treatment ranged from 2.86 to 24.8 cm^3 (mean 9.17 cm^3; SD 5.9). The TV at the latest follow-up was 1.1–12.4 cm^3 (mean 4.9 cm^3; SD 3.7) suggestive of 46.6% volume reduction ($p < 0.006$). On a paired sample statistical analysis, TV showed significant volume reduction (mean 43.8%) in patients with longer follow-up (> 36 months). TV reduction (mean 36.3%) was also observed in patients with a shorter follow-up period (< 36 months), but it was not statistically significant ($p = 0.32$) (Figs. 4 and 5). On the subgroup analysis, CSH showed the maximum TV reduction followed by cavernous sinus schwannoma (CSS) and CSM. CSH starts showing volume reduction even at 6 months (Fig. 6). There was 58.1% (mean) volume reduction in patients with CSH followed up for a < 36-month period, which improved to

Table 1 Patient demographics, dosimetry, and tumor volume reduction after single-fraction gamma knife radiosurgery

Patient	Age	Sex	Diagnosis	TV at treatment (cm³)	Prescription isodose (Gy)	Interval b/w t/t and the latest follow-up (months)	TV at the latest follow-up (cm³)	Pre-GKRS signs and symptoms	Response
1	42	F	CSM	5.04	15	96	1.98	- Headache - Partial ptosis - Restricted EOM	- No headache - No ptosis - Partial improvement
2	50	F	CSH	5.36	15	19	NA	- Headache - Ptosis - Restricted EOM	- Partial improvement - No ptosis - Complete recovery
3	48	F	CSM	14.22	8	36	12.38	- Pain over the left side of face (V2 and V3 distribution); TN	- Partial improvement
4	17	F	CSH	16.98	14	38	8.2	- Ptosis - Restricted EOM	- No ptosis - Partial recovery
5	47	F	CSM	5.79	13	23	5.42	- Headache - Restricted EOM	- Complete improvement - Partial recovery
6	30	F	CSM	9.98	24	4	NA	- Headache - Ptosis - Restricted EOM	- Partial improvement - No response - No response
7	56	F	CSH	7.66	14	36	2.5	- Ptosis - Restricted EOM - Homer's syndrome	- Complete recovery - Partial recovery - Partial recovery
8	39	M	CSM	24.8	13	9	NA	- Proptosis - Restricted EOM - Reduced visual acuity	- Reduced - No response - No improvement
9	40	F	CSM	2.86	14	24	2.4	- Headache - Partial ptosis - Abducens palsy	- Partial improvement - No response - Partial recovery - No diplopia
10	50	F	CSM	5.97	14	5	4.7	- Headache - Diplopia - Reduced vision	- Complete improvement - No diplopia - No improvement
11	38	F	CSS	3.25	14	36	1.9	- Abducens palsy	- No diplopia
12	33	F	CSH	15.1	15	13	3.47	- Headache - Abducens palsy	- Partial improvement - No diplopia
13	64	F	CSM	10.51	10.5	6	14	- Partial ptosis - Epiphora and pain on the right side of face; TN	- No improvement - No improvement
14	30	F	CSH	5.8	4.9	5	15	- Partial ptosis - Abducens palsy	- Partial recovery - No diplopia
15	67	M	CSH	9.59	5.38	4	12.5	- Headache - Abducens palsy	- No improvement - No improvement, persistent diplopia
16	24	F	CSH	3.74	1.14	3	13	- Headache - Restricted EOM - Diplopia	- Complete improvement - Complete recovery - No diplopia

b/w between, *cm³* cubic centimeters, *CSM* cavernous sinus meningioma, *CSH* cavernous sinus hemangioma, *CSS* cavernous sinus schwannoma, *EOM* extraocular movements, *F* female, *GKRS* gamma knife radiosurgery, *Gy* gray, *M* male, *NA* not available, *TN* trigeminal neuralgia, *TV* tumor volume, *t/t* treatment

Fig. 2 Flowchart showing the number of studies and patients included in the analysis (CSH cavernous sinus hemangiomas, CSM cavernous sinus meningioma, CSS cavernous sinus schwannoma, GKRS gamma knife radiosurgery)
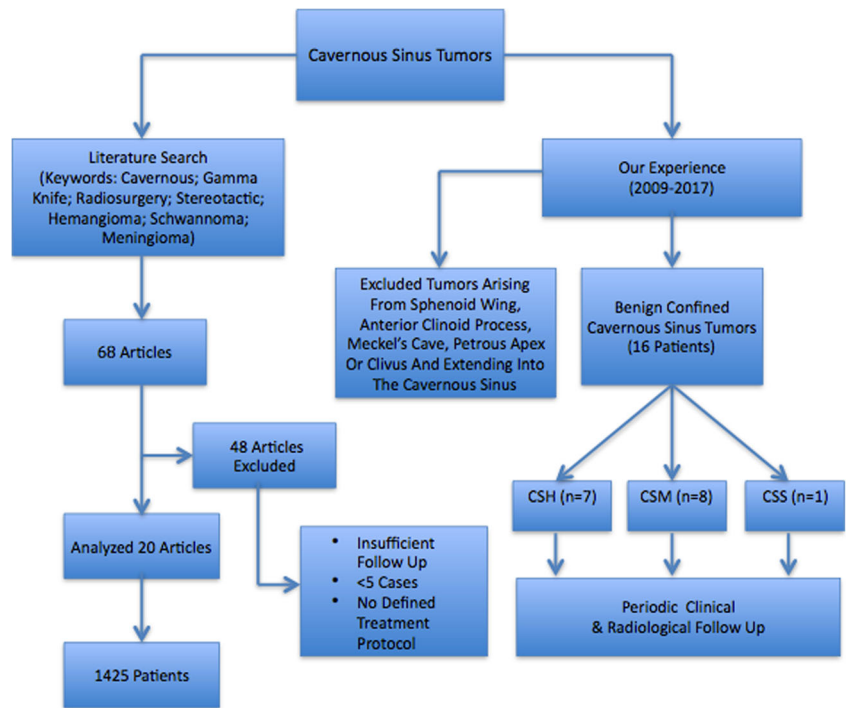

64% (mean) in patients with a > 3-year follow-up. There was only one patient of CSS in our study who showed 41.5% volume reduction at a 24-month follow-up (Fig. 7). Patients with CSM showed lesser volume reduction at both short- and long-term follow-ups (8.4 and 25.4%, respectively), but they reported clinical improvement in the form of relief of a head-ache and improved range of extraocular movements (Figs. 8 and 9). One patient of meningioma showed out-of-the-field tumor growth but did not consent for further radiology. There was no case of malignant transformation.

Discussion

CSTs remain intertwined with critical neurovascular structures that frequently invade the cranial nerve fascicles or encompass

Fig. 3 Clinical response after gamma knife radiosurgery for various cavernous sinus tumors (CSH cavernous sinus hemangiomas, CSM cavernous sinus meningioma, CSS cavernous sinus schwannoma, GKRS gamma knife radiosurgery)
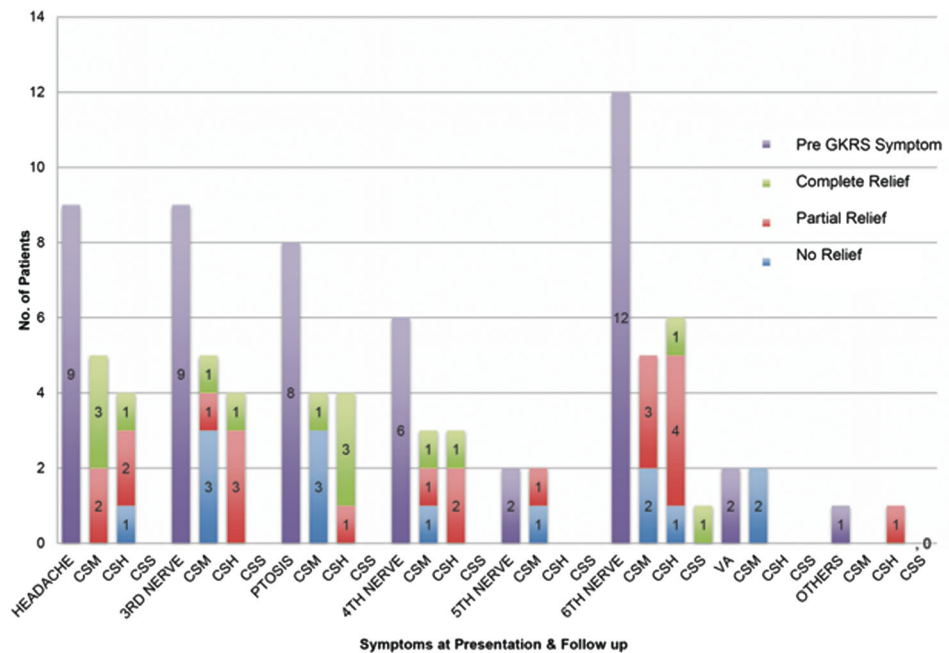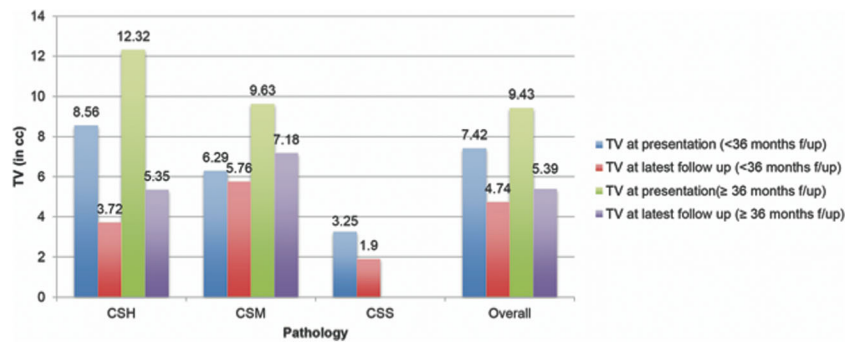
Fig. 4 Radiological response of confined cavernous sinus tumors after gamma knife radiosurgery at short (< 36 months) and long (≥ 36 months) terms (CSH cavernous sinus hemangiomas, CSM cavernous sinus meningioma, CSS cavernous sinus schwannoma, GKRS gamma knife radiosurgery, TV tumor volume)

the internal carotid artery, making aggressive surgical resection formidable. The reported tumor control rate and clinical outcome remain highly variable (Table 2). As most of the patients receive GKRS as a primary treatment modality, the first step in management is to establish the diagnosis of CST on radiologic parameters (Table 3).

Radiosurgical attributes of individual CST

CSH

CSH constitutes 1–3% of all parasellar lesions, frequently observed in females in the fourth to sixth decades of life [2, 29]. CSH is considered histologically distinct from intracerebral cavernous hemangiomas [12]. The highly vascular nature of CSH has led to significant intraoperative and postoperative complications, even death [25]. CSH takes origin in between the two layers of the dura mater on the lateral wall of the cavernous sinus causing direct compression over the cranial nerves. It usually presents with a headache, diplopia, facial numbness, visual disturbances, and seldom incidentally [51, 52, 55]. The incidental detection in a few patients demonstrates that the cranial nerves may adapt to the stretch in view
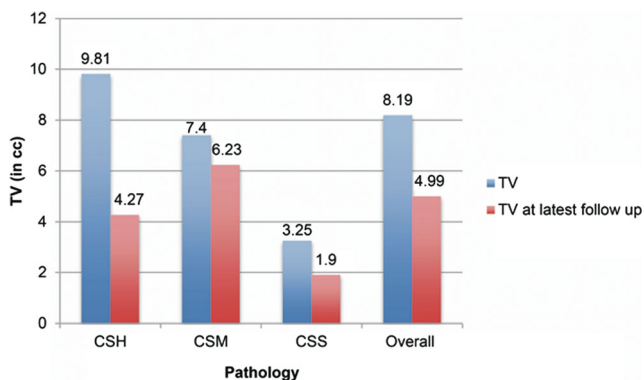

Fig. 5 Comparative radiological response of various cavernous sinus tumors after gamma knife radiosurgery (CSH cavernous sinus hemangiomas, CSM cavernous sinus meningioma, CSS cavernous sinus schwannoma, GKRS gamma knife radiosurgery, TV tumor volume)

of the slow growth of the tumor. CSH has a very low propensity to present with autogenous hemorrhage [4, 12, 20]. Most of the small CSHs are supplied by the meningohypophyseal trunk while tumors extending to the middle cranial fossa are additionally supplied by middle meningeal and accessory meningeal arteries.

Various reports have mentioned a 8–19 Gy marginal dose depending on the TV and distance from the eloquent structures (Table 2, Fig. 6) [7, 29, 36, 46, 56]. CSH shows rapid tumor resolution within 2 years of SRS [16, 17, 19, 38, 49, 50, 51, 53]. In our series, we observed that CSH shows early radiological improvement in comparison to CSM and CSS. In their seven-institute experience, Yamamoto et al. have recommended a peripheral dose of 14–15 Gy for controlling the growth of CSH and a dose of 10–12 Gy for tumor growth arrest [53]. The variable clinical presentation indicates that there might not be any direct correlation between TV, clinical presentation, earlier surgical attempt, and response to different dosages [55]. Clinical response to GKRS remains quite uncertain. Some patients show delayed response even by 4–5 years of treatment (Table 2, Additional Table 1) [55].

CSM

CSMs are rare intracranial tumors with an incidence of five per million population, most commonly in the middle-aged females [13, 22, 34, 45]. CSM remains adherent to the surrounding structures, viz. bone, dura, sinuses, and carotid wall, forbidding gross total resection (GTR) (range 20–76%) [8–10, 41]. Primary GKRS is an acceptable treatment modality for CSM up to 3 cm in maximum dimension and as an adjuvant treatment modality for lesions more than 3 cm. The surgical curability rates are also not impressive as permanent nerve deficits have been reported in a significant percentage of patients (8–26%) [14, 26, 27, 42, 54], and the recurrence rates were as high as 38% at 5 years after subtotal resection and 9.6% after total resection. Most CSMs are WHO grade I (90–97%) tumor [13, 26], while the exact percentage for atypical
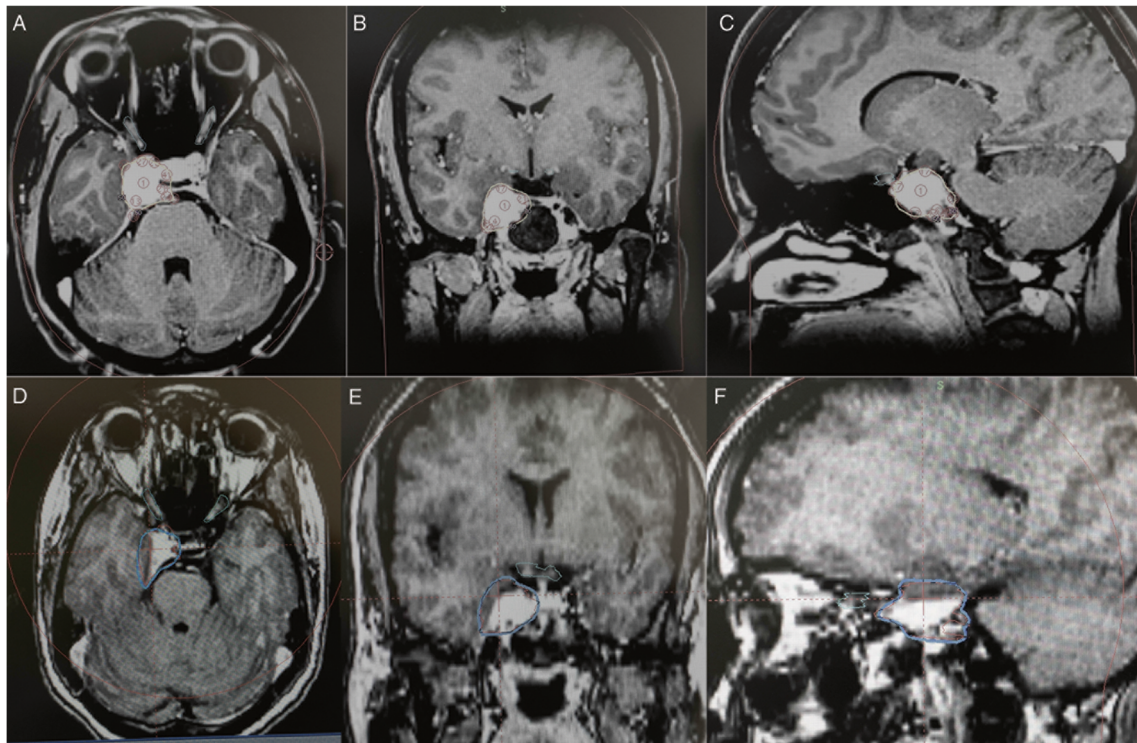
Fig. 6 Short-term radiological response in 5.8 cm³ cavernous sinus hemangiomas showing TV reduction at a 10-month follow-up (**a**–**c** pre GKRS: axial, coronal, and sagittal images; **d**–**f** corresponding images)

or malignant meningioma remains unaccounted. The reported outcome is better for primary radiosurgery than adjuvant therapy after subtotal resection [27]. In their experience with 111 patients of benign CSM, Hasegawa et al. [14] observed that out-of-the-field tumor failures were either recurrent lesions or extensive lesions in which the dural margin could not be differentiated from normal tissue or postoperative changes. Most of these failures were controlled with repeat GKRS. An interesting finding mentioned by this group is that patients with "in-the-field failure" did not demonstrate any atypical or anaplastic changes but were biologically aggressive benign tumors [14]. As the histopathology remains the same in both circumstances, the attributable cause might be difficulty in the radiologic definition of the tumor as a fat signal or meningeal enhancement might be confused with the tumor [27]. Though the definition of tumor control remains variable, the 5-year tumor control rate of patients primarily managed with GKRS remains impressive in the range of 95–96% (Table 2, Additional Table 1) [27, 39, 42].

CSSs

Majority of the CSSs arise from the trigeminal nerve. They either take origin in the Gasserian ganglion or extend from the posterior cranial fossa into the cavernous sinus. Rarely, they arise from other cranial nerves such as the oculomotor or abducens nerve. CSSs show better radiosurgical control in comparison to CSM (Fig. 7). Post GKRS, CSSs start showing loss of central contrast enhancement after 6–12 months, which is a predictive marker of long-term tumor control [32]. Most of the series report a successful outcome with a 12–14 Gy marginal dose (Table 2, Additional Table 1).

Fig. 7 Benign confined cavernous sinus schwannoma (**a** pre GKRS, **b** 2-year follow-up image showing significant TV reduction)
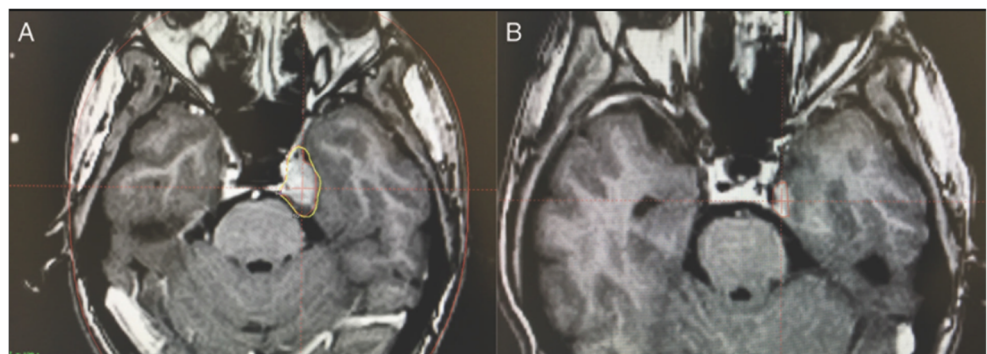
Fig. 8 Long-term response (6 years) after gamma knife radiosurgery for cavernous sinus meningioma (volume 5.1 cm^3; pre GKRS). **a** Axial cut showing homogeneous contrast enhancement. **b** Follow-up image showing significant TV reduction (follow-up volume 1.9 cm^3). **c, d** Corresponding coronal cuts, pre-GKRS and follow-up MRI. **e, f** Corresponding sagittal cuts, pre-GKRS and follow-up MRI
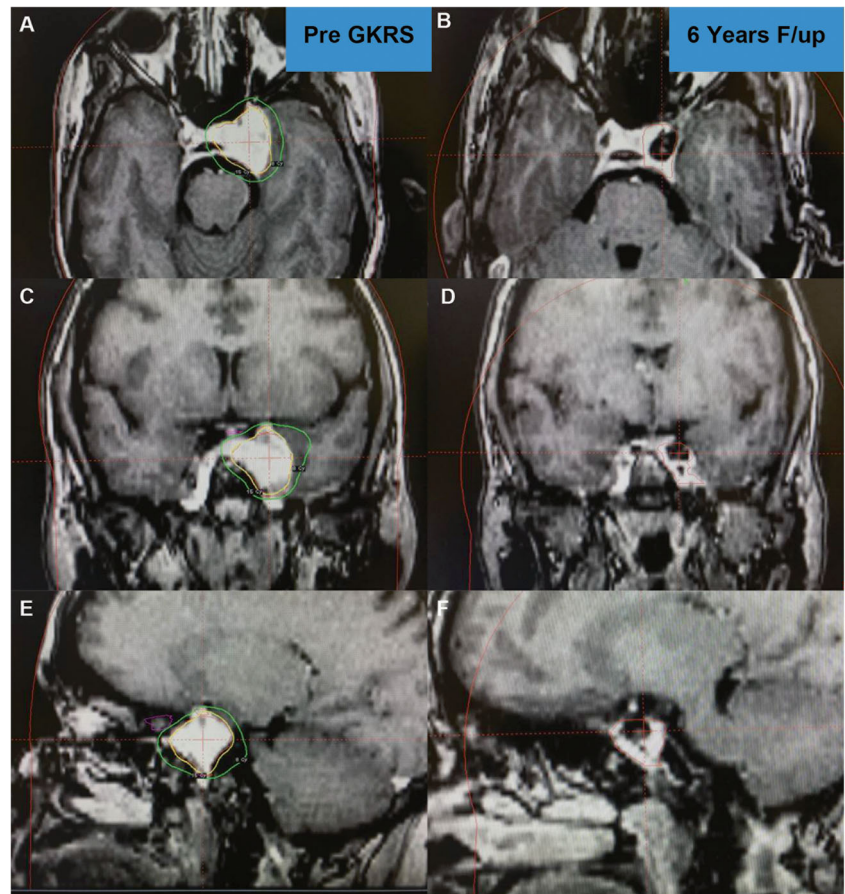
Treatment outcomes of GKRS for CSTs

Cranial neuropathy (Table 2)

The cavernous sinus lies at the cross road of important nerves, vessels, visual pathway, and the brainstem. Few lesions expand the sinus such as CSM while some compress it from the side such as CSH. Accordingly, nerves might be spread over the tumor or they might be in the substance of it. It is practically unavoidable to completely safeguard these neurovascular structures from radiation exposure [25]. The reported rate of new cranial neuropathies after GKRS reaches
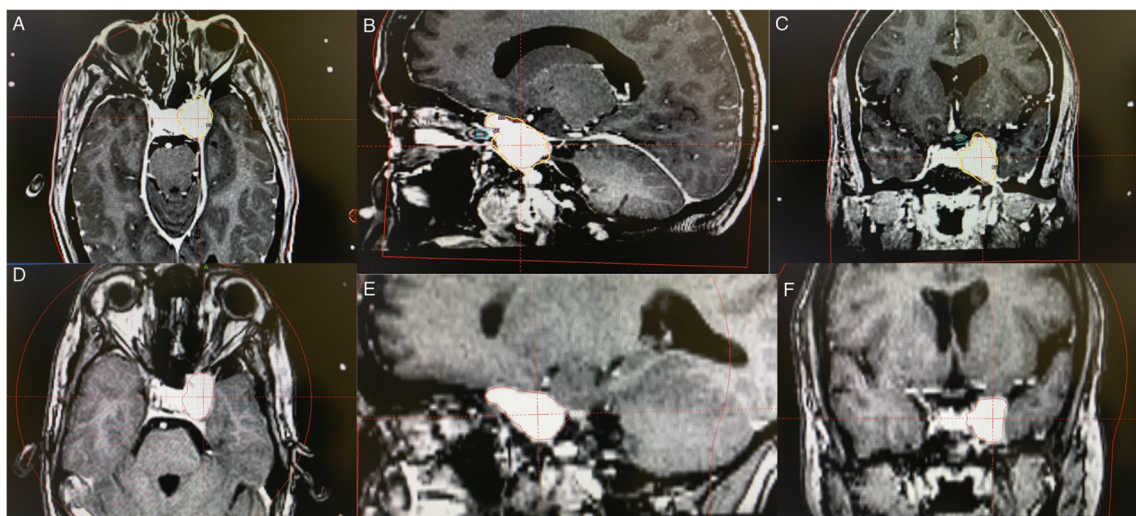
Fig. 9 Pre-GKRS (**a**–**c**) and follow-up (**d**–**f**) contrast-enhanced MRI images of cavernous sinus meningioma showing static tumor volume after a 3-year follow-up

Table 2 Comparative evaluation of gamma knife radiosurgery for various cavernous sinus lesions

Study	Year	Study design	Machine model	Total number of patients	Mean volume (cm³)	Mean prescription dose (Gy)	Mean follow-up (months)	Tumor control rate (%)	Cranial neuropathy (new onset or worsened) (%)
Hayashi et al. [15]	2012	R	4C	120	17.5	15.9	47	98	7
Wang et al. [52]	2012	R	NA	59	1.5–51.4	10–19	49.2	93.2	1.7
Liu et al. [32]	2005	R	B	175	0.32–29.8	15–45 (26.7)	32.5	94	7.8
Iwai et al. [18]	1996	P	4C	43	14.7	8–15 (11)	49.4	90.5	7
Duma et al. [11]	1993	NA	NA	34	5.2	16	26	100	6
Liscak et al. [31]	1999	NA	NA	67	7.8	12	19	100	0
Chen et al. [6]	2001	R	G	69	4.7	15	40.5 months	99	0.01
Roche et al. [43]	2002	P	G	80	5.8	14	30.5 months (12–79)	95	0.01
Shin et al. [47]	2001	NA	NA	40	4.3	18	42	80	2.5
Kuo et al. [21]	2004	R	U, C	139	3.4	15	42	97.8	2.2
Lee et al. [27]	2002	R	U, B	167	6.5 (0.5–52.4)	13.3 (11–14)	39 months (2–145)	96.9	0.05
Li et al. [30]	2012	P	C	16	30.4 (1.5–61.5)	11–14	21.5	87.5	0.00
Yamamoto et al. [53]	2010	P	NA	30	11.5 (1.5–51.4)	14 (10–17)	53	50	3.3
Wang et al. [55]	2016	P	C	32	30.53 (2.5–78.6)	14.22 (11–16)	30.2 months (12–67)	96.5	0
Lee et al. [25]	2017	R	NA	31	9.3 (1.5–42.1)	12.6 (12–19)	54 months (6–200)	>50	0.03
Hafez et al. [13]	2015	R	4C	62	5.7 (1.8–12.4)	<14.4	36 months (24–96)	96	0.02
Hasegawa et al. [14]	2007	R	B	115	13.8 (0.6–121.8)	13 (7.5–17)	62 months (8–144)	88	NA
Pollock et al. [42]	2013	P	NA	115	9.3 (1.3–42.2)	16 (12–20)	89 months	95	12
Chou et al. [7]	2010	R	4C	7	7.6 (2.9–23.1)	16.9 (16.1–18.9)	22 months (6–156)	82	NA

cm³ cubic centimeters, *CSH* cavernous sinus hemangioma, *Gy* gray, *NA* not available, *P* prospective, *R* retrospective

Table 3 Characteristic radiological features for differential diagnosis of various cavernous sinus lesions

Lesion	T1WI	T2WI	FLAIR	T1 Gad
Meningioma	Hypo- to isointense	Hypo- to isointense	Heterogeneously hyperintense	Moderate homogenous enhancement
Pituitary adenoma	Hypo- to isointense	Iso- to hypointense	Heterogeneously hyperintense	Moderate variable enhancement
Nerve sheath tumor	Hypointense	Iso- to hyperintense	Heterogeneously hyperintense with suppression within cysts	Mild to moderate heterogeneous enhancement
Hemangioma	Hypointense (hyperintense in case of slow flow/static blood)	Hyperintense	Homogenously hyperintense	Moderate to brilliant enhancement

Lesion	DWI	SWI	Ancillary features
Meningioma	Mild to moderate diffusion restriction	Rare hemorrhages Calcification may be present	Early contrast uptake with delayed egress ("mother in law" sign) on dynamic CEMRI - ± dural tail - Compresses and narrows ICA
Pituitary adenoma	No diffusion restriction	Hemorrhages may be present	- Epicenter in the sella turcica - Iso- to hyperperfused on SPECT
Nerve sheath tumor	No diffusion restriction	Tumoral microhemorrhages may be present	- Extension along the course of the involved nerve bundle
Hemangioma	No diffusion restriction	Uncommon hemorrhages	- Progressive centripetal filling on dynamic CE MRI - The ICA is usually encased but without narrowing

CE contrast-enhanced, *DWI* diffusion-weighted imaging, *FLAIR* fluid-attenuated inversion recovery, *ICA* internal carotid artery, *MRI* magnetic resonance imaging, *SWI* susceptibility-weighted imaging

up to 19% [15]. A new-onset or worsened cranial neuropathy may be secondary to direct irradiation of the nerves or transient enlargement of the lesion (common in CSM and CSS). The third and sixth cranial nerves are particularly vulnerable. Other possible reasons are cranial nerve location inside the target volume receiving high-dose irradiation and radiation toxicity after repeated GKRS [15]. These complications have lessened after the introduction of the Perfexion model due to its better precision and conformity in comparison to the earlier models. How do these nerves respond to radiation remains debatable, as tumor nerve relation is complex, exact radiation dose delivered cannot be definitely defined, and tumor response to radiation remains variable [43].

Post-GKRS visual deterioration may be progressive or sudden. Radiation-induced optic neuropathy (RION) is attributable to radiation spillage on the visual pathway [23], which may manifest after a mean latency period of 13 months (6 months–3 years) [3]. RION may present as anterior optic neuropathy in the form of pale edema of disc with incidental splinter hemorrhages or posterior optic neuropathy with a loss of visual acuity/field defects [24]. A sudden-onset visual deficit is due to a compressive phenomenon such as tumor enlargement with direct pressure at the annulus of Zinn or vascular compromise. Lee et al. reported visual deterioration in 2% of cases secondary to a higher marginal dose (12 Gy) to visual apparatus [27]. The dose-volume relation of the optic nerve revealed a safe dosage in the range of 8–10 Gy in single-fraction treatment. In their series of 222 patients receiving

GKRS for lesions abutting the anterior visual pathway, Leavitt et al. reported RION in 1% of patients receiving > 8 Gy radiation to the anterior visual pathway [23]. Skeie et al. reported 2% incidence of RION in their 100 patients of CSM [48]. Leber et al. reported 26.7% optic neuropathy when radiation dose to visual pathway ranged from 10 to 15 Gy [24]. However, Pollock et al. have prescribed 11–12 Gy radiation to large CSMs abutting optic apparatus but have not reported visual deterioration even on a long-term follow-up [42]. Mayo et al. mentioned that the incidence of RION is rare at < 8 Gy, increases for 8–12 Gy, and becomes > 10% for 12–15 Gy exposure to the anterior visual pathway after single-fraction radiosurgery [23, 35]. Small volumes of the anterior visual pathway (2–4 mm^3) can tolerate radiation doses up to 12 Gy with a low risk of RION [32].

The time of development of post-radiosurgery clinical improvement or cranial neuropathy remains debatable (range 2 months–3 years) (Table 2) [1]. Most of the series reported significant clinical improvement in the oculomotor nerve after GKRS [24, 27, 37, 43]. The trigeminal nerve appears to be more susceptible to adverse effects of radiation [27]. Tumor-related secondary facial pain gives a variable response to radiation in comparison to typical facial pain observed with trigeminal neuralgia. Morita et al. observed severe trigeminal neuropathy or dysesthesia in patients receiving > 19 Gy to Meckel's cave [37]. Roche et al. reported that > 50% of patients with trigeminal neuralgia either improved or recovered after GKRS in patients with CSMs [43]. However, Chang et al. observed

that > 50% of patients report with recurrence of pain after initial symptomatic pain improvement in the follow-up period [5].

Exposure to mesial temporal lobe

Mesial temporal lobes are radiosensitive eloquent areas that need protection by a sharp dose fallout at the lateral margin of the cavernous sinus. Lee et al. reported complex partial seizures (CPSs) in two of 167 patients at an average of 16 months post GKRS [27]. Duma et al. reported CPS in two of 34 patients 16 months post GKRS, but the radiation exposure to the mesial temporal lobe in all the patients was < 12 Gy [11].

Vascular complications

Thrombosis of normal arterial vasculature has also been reported after GKRS for various indications including occlusion of the internal carotid artery (ICA) in cases of CSTs (Table 4) [1, 28, 40, 42, 43]. There is no safe dose defined to prevent vascular complications after GKRS. The inherent dose heterogeneity of a gamma knife plan might lead to accidental high-dose delivery to the artery (ICA in case of cavernous sinus lesions), which may vary from 13 to 30 Gy depending on the location of the hot spot in the lesion.

Tumor control

Studies have reported a 84–100% tumor control rate on long-term follow-up. There is no uniformity in defining tumor control for CSTs. The leading radiosurgical groups have considered either a volume change of 10% or a dimension change of 2 mm as significant. Improvement in cranial neuropathy is proportional to TV reduction. CSH shows the best volumetric reduction followed by CSS, pituitary adenomas, and CSM. Post-radiosurgical tumor response should be considered an important clinical surrogate marker of pathological differential of CSH. CSH shows prompt radiosurgical response within 6–12 months of radiation with volume reduction to the extent of 89% in comparison to 29% of CSM [4]. Hafez et al. in their series of 62 CSM patients have reported a > 96% tumor control rate with 14.4 Gy marginal dose [53] (Table 2, Additional Table 2).

Up to 15% of CST cases show progressive tumor growth despite previous GKRS [39]. A transient increase in TV has been reported more with CSS followed by pituitary adenomas, CSHs, and CSMs. There are several reasons for the progressive growth of a tumor such as insufficient dose, inherent resistance of tumor, radiologic artifacts, suboptimal target selection, inhomogeneous dose distribution, radiation-induced changes, or malignant transformation. Targeting a homogeneity index (HI) more than 0.5 helps in providing hot spots inside the target volume, homogeneous dose distribution, better conformity, significant tumor shrinkage, and lesser chances of cranial neuropathies [15]. The higher failure rate in earlier series might also be attributable to an inferior planning system (Kula).

Nuances of radiosurgical planning for CSTs

It is important to evaluate the direction of displacement of the neurovascular structures in relation to the tumor. The value of a good radiology cannot be over emphasized. It is very difficult to separately outline individual nerves while planning. However, it is presumed that the cranial nerves are displaced rather than engulfed by benign CSTs; the effective dose to these nerves is considered equal to the calculated marginal dose [23, 33]. The shots are placed so that the isodose line does not contact a significant length of the nerve. Ivanov et al. have recommended avoiding incorporation of the lateral wall of the cavernous sinus into the 80% isodose line [16]. A plan is designed in such a way that the vital eloquent structures receive the recommended tolerable dose, i.e., ≤ 8 Gy for the visual pathway, ≤ 12 Gy the to brainstem, ≤ 4 Gy to the cochlea, ≤ 30 Gy to the ICA, and ≤ 14 Gy to the motor nerves. A good conformity and dosimetry planning is the key to achieve good results after GKRS [4].

If the visual pathway cannot be separately delineated from the tumor with a safe margin, the patient should be considered for an alternate treatment option such as debulking surgery or intensity-modulated radiation therapy (IMRT) [11]. In cases of tumors abutting optic apparatus, the marginal dose might be reduced to 8–10 Gy. With these low doses, complete remission is not achieved, but tumors do cease further growing [26].

Table 4 Vascular complications following gamma knife radiosurgery for cavernous sinus lesions

Author	Indication	Dose delivered to ICA (Gy)	Latent interval	Clinical complication secondary to ICA occlusion
Abeloos et al. [1]	CSM	22.3	40 months	Asymptomatic
Roche et al. [43]	CSM	36	14 months	Transient facial palsy
Lim et al. [28]	Residual pituitary adenoma encasing the cavernous ICA	< 20	4 years	Hemiparesis and facial palsy
Pollock et al. [42]	CSM	Not mentioned	Not mentioned	Frontal and basal ganglia infarct

CSM cavernous sinus meningioma, *ICA* internal carotid artery, *Gy* gray

Alternatively, the marginal dose should be kept a small distance away from the optic apparatus [40]. As most of the CSTs are irregular in shape, complex dose planning with multiple isocenters is required to maintain sharp dose fallout and conformity. The Pittsburgh group advocates the use of customized beam blocking pattern to restrict the dose from the optic apparatus by blocking the beams [26, 42].

Radiobiologically, large vessels are considered radioresistant (Table 4). Radiological planning should be done to keep the hot spots away from the vascular lumen preventing maximum dose delivery to the vessel. Special emphasis should be given to the patients receiving re-irradiation. There are chances of enhancement of tumor and the peripheral margins after surgery, which need to be considered while defining lesions during planning. In such cases, the treatment should be done after nearly 2–3 months of surgery [7].

Objectives of treating a cavernous sinus lesion/is there a role of proactive radiosurgery!

The treatment option and the modality of treatment remain a debatable issue in incidentally detected CSTs. These lesions can be monitored with regular follow-up or with proactive radiosurgery. Any clinical deterioration adversely affects quality of life and chances of recovery. Wang et al. treated seven asymptomatic incidentally detected cases of CSH, and the results were favorable [52]. Though the definite diagnosis of CST remains quite variable, it is usually not necessary to histopathologically confirm the lesion, as all of these tumors are good radiosurgery candidates [9]. The impressive result of GKRS on CSH has prompted its role as a proactive treatment option analogous to initiation of dopamine agonist therapy as opposed to surgical resection for newly diagnosed patients with prolactinomas and visual loss [4].

Limitations of study

The main limitation is the retrospective design and relatively small number of the patients. On virtue of a single-center study, our analysis may suffer from the reference, selection, and observer bias. We did not evaluate individual cranial nerve sensitivity for radiosurgery. But, the strengths of our study are regular follow-up with clinical and radiological evaluation and nearly homogeneous patient population.

Conclusion

It can be concluded that GKRS is the most suitable option on virtue of its minimally invasive nature, optimal long-term tumor control, improvement of cranial neuropathies, cost-effectiveness, favorable risk-benefit ratio, and minimal long-term complications. It should be acknowledged that some questions still remain unanswered such as tolerance of cranial nerves, mesial temporal lobes, carotid vasculature, and long-term risk of tumorigenesis.

Compliance with ethical standards

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