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Gamma Knife Radiosurgery for Cavernous Sinus Meningiomas: Analysis of Outcome in 166 Patients

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Abstract
Objectives: The outcomes of Gamma Knife radiosurgery (GKRS) for cavernous sinus meningioma (CSM) are presented, and factors possibly affecting outcome are investigated. ***Methods:*** The medical records and imaging and procedural reports of 166 patients with CSM were retrospectively reviewed. Demographic data, procedural data, symptomatic improvement, radiological regression, and progression-free survival (PFS) rates were evaluated. ***Results:*** There were 124 women and 42 men; including 44 postoperative and 122 primary GKRS cases. Mean follow-up was 32.4 months. Mean marginal dose was 13 Gy. Symptomatic improvement was seen in 40.4%, while neurologic deterioration occurred in 9.6%; 50% remained symptomatically stable. Radiological regression was noted in 57.2%; the tumor remained stable in 35.5%, and 7.2% of the patients experienced tumor progression. The actuarial 5- and 10-year PFS rates were 90.1% (±3.3) and 75.8% (±8.8), respectively. History of previous surgery or radiotherapy were associated with lower symptomatic improvement. Higher tumor coverage and isodose lines were accompanied with better radiological prognosis. However, a history of conventional radiotherapy, presence of facial sensory deficits at presentation, a higher tumor volume, and tumor extension to the suprasellar compartment affected the radiologic outcome negatively. ***Conclusion:*** This study revealed a high efficacy and safety for GKRS in both postoperative and primary GKRS patients. Achievability of a good profile of tumor coverage and isodose lines at radiosurgical planning predict a better outcome.

Introduction

Cavernous sinus (CS) tumors comprise around 1% of all brain tumors, half of which are meningiomas. Parasellar and cavernous meningiomas, although being considered as benign and usually WHO grade I tumors, may introduce a real treatment challenge due to their location, where complete surgical resection carries the risk of various neurovascular injuries [1–4].

Prodigious advances in the microsurgical armamentarium and techniques and better understanding of the

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anatomical nuances in recent decades have enthused the skull base surgeons to perform surgeries in deeper complex neuroanatomical areas with a higher expectancy for total tumor removal and thus a better tumor control. However, this enthusiasm has declined down to a plateau when it became clear that there is a high burden on quality of life with an aggressive surgical approach while microscopic infiltration of neurovascular elements cannot be eliminated in CS by surgery alone [4–6]. These observations paved the road for reconsideration of radiotherapeutic approaches as the sole or adjunctive treatment modalities. Radiosurgery, in this way, turned out to be related to long-term control of the tumor [7–15].

Achieving a long-term tumor control versus saving neurovascular elements and maintaining a good cranial nerve function are the two important goals that can be reached by stereotactic radiosurgery alone or in combination with a more conservative surgery. In this paper, we present the data and outcome of patients with cavernous meningioma treated with Gamma Knife (GK) radiosurgery (GKRS) in the sole GK center of the country.

Patients and Methods

In this retrospective study, among 172 cavernous sinus meningioma (CSM) patients who underwent GKRS performed by the senior authors, 166 patients followed ≥6 months were entered into the study (none of the 6 cases excluded had a fatal surgical outcome). These patients were treated with either primary or postoperative GKRS during 2002 to 2013. In patients without previous surgery and hence no histological confirmation, the diagnosis of meningioma is made by its typical radiological features, i.e., hypo- to isointensity in T1W, iso- to hyperintensity in T2W, extensive and homogenous enhancement, and presence of a dural-based extension pattern. Cavernous meningioma was defined as a tumor with its epicenter in the CS area in magnetic resonance images.

Indications for Radiosurgery

Significant tumor remnant after surgery, radiological or symptomatic progression in nonoperated patients, tumor recurrence/regrowth, and patients that were not suitable for surgery (e.g., underlying disease) were considered for GKRS.

Radiosurgical Dose Planning

The GK system “Gamma Plan type C” was employed. For all patients, a stereotactic Leksell frame was affixed to the patient’s head after administering local anesthetics. MRI was performed with the frame in position to determine the stereotactic coordinates of the treatment target. Computer planning was conducted according to the GK planning program. Less than 10 Gy were acceptable for the optic system. Radiosurgery was performed using a 201 cobalt-60 source. The dose was adjusted for patients with a history of previous radiotherapy.

Follow-Up Protocol

The patients were seen and evaluated by MRI every 6 months during the first 2 years of GKRS, annually thereafter for 3 years, and every 2–3 years afterwards. Tumor progression or regression was defined as >15% change in tumor volume in the last postoperative MRI. Tumor volume in post-GKRS follow-ups was calculated using the ellipsoid formula: $a \times b \times c / 2$.

Statistical Analysis

Statistical results were reported as means ± SD for quantitative variables and percentages for categorical variables. The χ^2 test was used for nominal variables and the *t* test or ANOVA was used for numerical variables with two or more categories, respectively. ANCOVA (analysis of covariance) was used to evaluate confounding factors in ANOVA tests. The Tukey post hoc test was employed to determine relationships between different categories. To investigate different operating factors by multivariable logistic regression analysis, those with values of $p < 0.2$ in individual tests were analyzed. Receiver-operating characteristic curves based on the maximization of the Youden index rounded to the nearest whole number were used to determine cutoff values. The Youden index, equal to the sum of sensitivity and specificity minus one, is used for calculating optimal thresholds. Survival analysis was performed using the Kaplan-Meier method, the log-rank (Mantel-Cox) test for categorical data, and the Cox proportional hazard test for continuous data. Multivariate analysis was also performed by the Cox proportional hazard test. Values of $p < 0.05$ were considered statistically significant. All the statistical analyses were performed using SPSS (version 22.0; SPSS Inc., Chicago, IL, USA).

This study is designed and implemented in accordance with the Helsinki Declaration of the World Medical Association. All patients who underwent radiosurgery have signed an informed consent. The study was approved by the local ethics committee of the research center.

Results

Demographic Data

A total of 166 patients with CSM entered the study. There were 124 women and 42 men with mean ages of 49.6 and 55 years, respectively (ranges between 16–79 and 23–81 years, respectively; 73% of the patients had GKRS as their first treatment modality. The mean and the median follow-up were 32.4 and 24 months, respectively (range: 6–120 months). Demographic data, previous treatments, and detailed follow-up data are summarized in Table 1. Eighty percent of the patients (133 patients) presented with symptoms of cranial nerve deficits, especially those of ocular movement. Details on cranial nerve involvement at presentation are summarized in Table 2.

Table 1. Summary of the study patients' characteristics and outcome

Patients, *n*	166
Females	124
Males	42
Female/male ratio	2.9
Mean age, years	50.9 (16–81)
Tumor extension	
Confined to cavernous sinus	43 (25.9%)
Middle fossa	53 (31.9%)
Petrous and petroclival junction	50 (30.1%)
Suprasellar compartment	24 (14.5%)
Tentorium	13 (7.8%)
Orbit	9 (5.4%)
Others	2 (1.2%)
Previous surgeries, *n*	
0	122
1	35
2	6
3	3
Conventional radiotherapy	9
Mean follow-up time, months	32.4 (6–120)
Mean tumor volume, cm^3	10 (0.6–56.9)
5-year progression-free survival, %	90.1
Radiologic outcome, %	
Regression	57.3
Stabilization	35.5
Progression	7.2
Symptomatic outcome, %	
Improvement	40.4
Stabilization	50
Deterioration	9.6
Factors associated with a worse radiologic outcome	
Lower radiosurgical tumor coverage	
Lower isodose line	
History of conventional radiotherapy	
Trigeminal sensory symptoms at presentation	
Factors associated with a worse symptomatic outcome	
History of previous surgery	
History of previous conventional radiotherapy	

Table 2. Cranial nerve deficits in the study patients at presentation

Cranial nerve	Gamma Knife radiosurgery		All
	primary	postoperative	
I	1	2	3 (1.8%)
II	23	15	38 (22.9%)
III	65	27	92 (55.4%)
IV	23	12	35 (21.1%)
V	31	11	42 (25.3%)
VI	55	20	75 (45.2%)
VII	18	7	25 (15.1%)
VIII	22	12	34 (20.5%)
Lower CN deficits	1	3	4 (2.4%)

Lower cranial nerve (CN) deficits (including IX, X, and XII) were observed only in tumors with major extension to the posterior fossa.

Table 3. Radiosurgical dosimetry

Maximal dose, Gy	
Mean	25.2
Range	17.9–40
Marginal dose, Gy	
Mean	13
Range	6–18
Isodose, %	
Mean	55.3
Range	28–75
Isocenters	
Mean	17.6
Range	3–49
Tumor coverage, %	
Mean	97.9
Range	90–100

Tumor Characteristics and GKRS Data

In 43 patients (38%), there were no tumor extensions outside the CS, while in others there were various combinations of tumor extensions (Table 1). There were also 2 unusual extensions, one into the subtemporal fossa and the other into the ethmoid sinus. There was no significant difference in mean tumor volume (overall = 10.02 cm^3) between previously operated and nonoperated patients (10.75 vs. 9.75 cm^3, respectively, $p = 0.450$). Of the 44 patients who underwent previous surgery, 4 patients has WHO grade II meningiomas, and 1 patient had grade III. No significant association between tumor grade and patient outcome was found.

Mean maximal and marginal doses were 25.2 Gy (range: 17.9–40 Gy) and 13 Gy (range: 6–18 Gy), respectively. Radiosurgical doses administered are summarized in Table 3. Dose planning was performed considering maximal tumor coverage, uniformity of the field, and minimal involvement of the critical structures such as the brain stem and optic apparatus (Table 3).

Table 4. Information on the patients with tumor progression

Patient	Age, years	Extension outside CS	Sex	Surgery	Radiotherapy	Max. dose, Gy	Volume, cm^3	Tumor coverage, %	Marginal dose, Gy	Follow-up, months
1	33	Mid+Sup	M	yes	no	40.0	41.2	97	14	27
2	35	Mid+Tent	F	no	no	23.8	7.9	99	15	36
3	42	Mid+Sup	M	yes	yes	26.0	17.9	96	13	19
4	43	none	F	no	no	17.9	2.6	96	12.5	16
5	46	Sup	F	yes	yes	27.0	9.3	92	13.5	84
6	49	Pet+Mid	F	yes	no	26.0	0.6	91	10.1	18
7	51	Mid+Sup	F	no	no	26.8	8.6	96	12	12
8	54	Pet	F	no	no	32.5	4.9	100	13	12
9	56	none	F	no	no	28.0	5.4	99	13	36
10	57	Sup	F	yes	no	30.0	23.5	94	12	60
11	59	Mid+Sup	M	yes	yes	27.0	24.2	99	13.5	60
12	81	none	M	no	no	21.5	41.2	97	14	48

Mid, middle fossa; Sup, suprasellar; Tent, tentorium; Pet, petrous and petroclival.

Tumor Control

Radiological Response

Tumor control (regression or stabilization of the tumor size) was achieved in 154 patients (92.8%): 95 (57%) patients showed radiological regression, and in 59 patients (35%), no tumor change occurred during the follow-up period. For the group with no change in tumor size, mean follow-up was 29.5 months (range: 6–120 months, and in 8 cases follow-up was <12 months). In 12 patients, tumor growth continued despite GKRS. Detailed information about tumor radiological data of the 12 patients with tumor progression is presented in Table 4.

Factors Associated with Radiological Outcome

The effects of various numerical variables (including radiosurgical dosing parameters, follow-up time, age, and time gap between diagnosis and GKRS) on radiological outcome were tested using one-way ANOVA. Only tumor coverage ($p = 0.033$) and isodose lines ($p = 0.042$) reached a significant level. In post hoc test, the patients with tumor progression had a lower tumor coverage in comparison with the two other groups ($p = 0.025$ and $p = 0.050$). There was no significant difference in terms of tumor coverage among the patients with tumor regression or stabilization ($p = 0.929$). When data were divided as radiologically improved versus nonimproved data, a lower tumor volume was associated with a higher chance of tumor regression (independent-sample *t* test, $p = 0.014$), which was confirmed in multivariate analysis.

To analyze categorical variables (including gender, history of radiotherapy, history of previous surgery, number of previous surgery procedures, tumor extension, and presenting symptoms), the χ^2 test was performed. History of radiotherapy, the presence of trigeminal sensory deficits at presentation, and extension to the suprasellar compartment were significantly associated with a worse radiological outcome ($p = 0.008$, $p = 0.019$, and $p = 0.004$, respectively).

Neurologic response

During the follow-up time, some symptom improvement occurred in 67 patients, while 16 patients experienced deterioration in some symptoms, and in others symptoms did not change. The radiological and symptomatic outcomes are summarized in Table 5.

Factors Associated with Neurological Outcomes

History of previous surgery or radiotherapy was associated with worse neurological outcomes ($p = 0.014$ and $p = 0.034$, respectively). Among the patients who underwent surgery and GKRS, those who had not received conventional radiotherapy had better symptomatic outcomes compared to those who had not (marginally significant, $p = 0.055$). Symptomatic outcomes were not correlated with radiological outcomes ($p = 0.283$).

Survival Analysis

Five- and 10-year progression-free survival (PFS) rates were 90.1% (±3.3) and 75.8% (±8.8), respectively (Fig. 1). Although PFS was higher in primary GKRS patients than postoperative patients, it did not reach significance ($p = 0.131$; log-rank test). When multivariate analysis was per-

Table 5. Summary of radiological and symptomatic outcome after Gamma Knife radiosurgery (GKRS)

Symptomatic outcome	All	Improved	No change	Worsening	New deficit
Cranial nerves					
I	3	0	3	0	0
II	38	5	32	1	0
III	92	48	38	3	3
IV	35	9	24	0	2
V	42	2	39	1	0
VI	75	9	64	0	2
VII	25	2	18	2	3
VIII	34	1	31	0	2
Lower CN	4	0	4	0	0
Radiological outcome	**All**	**Tumor regression**	**No tumor growth**	**Tumor control**	**Tumor progression**
All patients	166	95	59	154	12
Primary GKRS	122	71	45	116	6
Post-op. GKRS	44	24	14	38	6

Overall, 16 patients experienced deterioration in some symptoms, in 67 patients some symptoms improved, and in the remainder no change in symptoms occurred. Lower CN, lower cranial nerves including IX, X, and XII.

formed (Cox regression model), only tumor coverage was near to a significant level ($p = 0.071$).

Complications

Neurological complications were defined as a deterioration in symptoms or the occurrence of a new neural deficit after GKRS. Complications happened in 18 patients (10.8%), including cranial nerve complications in 16 patients and adverse radiation effects in 2 patients. The most common complications were permanent deterioration in diplopia and/or facial sensation (Table 5). Radiological progression was also observed in 12 patients. Five patients died during the follow-up period, all of them >4 years after GKRS for reasons unrelated to the treatment, but 1 patient who developed hydrocephalus underwent shunt placement and finally died of the shunt complications.

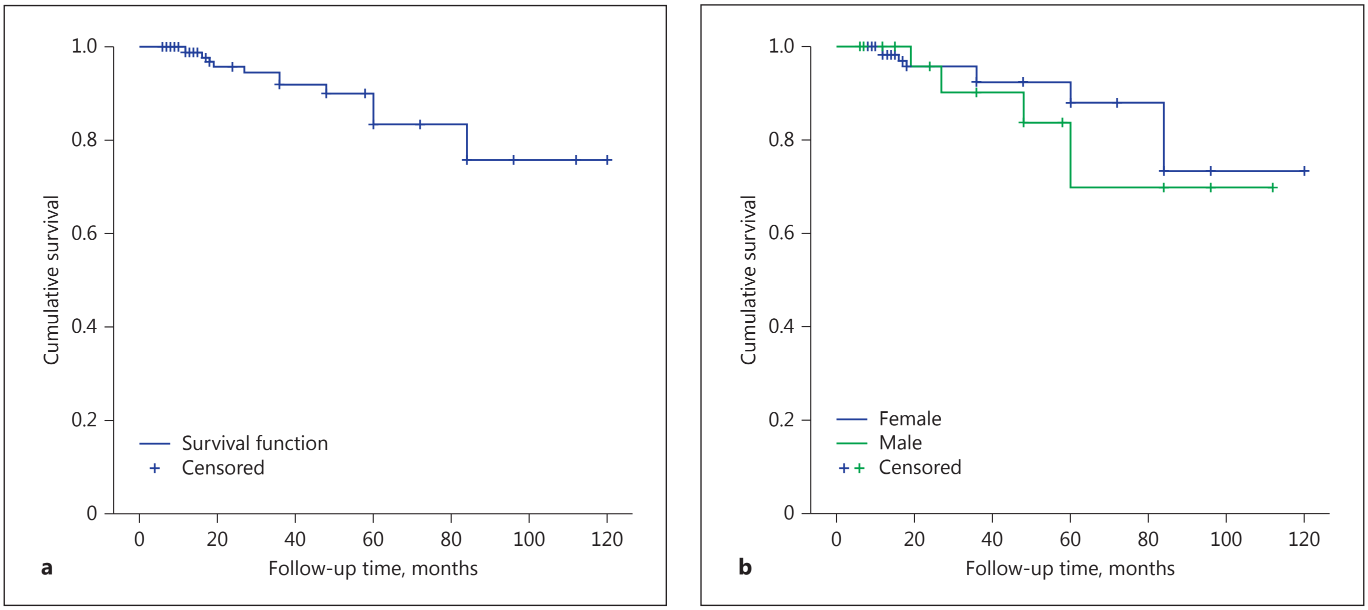
Discussion

CS is a space between the two layers of the dura mater in each lateral side of the sella turcica. Composed of venous channels, CS contains cranial nerves III, IV, VI, the first two branches of the trigeminal nerve, the internal carotid artery, and its branches to the pituitary gland. Therefore, although CSM is a benign tumor, it can cause significant morbidity. If tumor control cannot be achieved, it can be life limiting, with an average life expectancy of 2 years [14]. In CSM, the female/male ratio is higher than the usual 2:1 ratio of meningiomas [7, 8, 10, 14–19]. In our study, it was 2.9:1.

Recently, following technical and instrumental refinement, more and more patients underwent surgical treatment for the management of CSM. Total surgical resection of the intracavernous part of a meningioma, if not being impossible, is extremely difficult. Gross total resection in this situation has been reported to be achieved in only 20–76% of cases [4, 20]. Besides, in new surgical series, recurrence was remarkable, ranging from 9.6 to 25% even after gross total resection [1, 2, 4, 7, 21]. Mortality ranged from 2 to 7% and morbidity from 10 to 65% for these approaches [1–4, 12, 21]. High rates of recurrence and progression in microsurgical series have been shown to be the result of microscopic infiltration of the neurovascular structures of the CS by tumor cells [12, 22] that cannot be completely eliminated [7, 22, 23] and may necessitate an adjuvant radiation modality. In one of the last series, Nanda et al. [24] showed that complete resection has no effect on tumor recurrence, and they mentioned that outcome is better with GKRS plus surgery than with surgery alone.

Our study comprises 166 patients, and it is one of the largest series published about CSM (Table 6). We have achieved a control rate of 92.8% in a mean follow-up time of 32.4 months. Only in 12 patients, the tumor progressed. Deterioration in cranial nerves function was also considerably low (9.6%), and overall complications occurred in 10.8%. In the last 2 decades, studies have been published that showed the efficacy of GKRS in CSM control [7, 9, 10, 15–19, 24–31]. In these studies, PFS rates as well as follow-up times and dose planning vary. The reported PFS rate in these studies ranges from 80 to 100% after 5 years and from 73 to 98% after 10 years (Table 6). New cranial nerve deficits in these studies vary from 0 to 25%. Although a thorough comparison may not be possible among these studies, they all emphasized the efficacy and safety of radiosurgery in long-term tumor control.

In this study, factors that affect patient prognosis were considered separately in two fields: radiological response and symptomatic improvement. A history of previous radiotherapy had a negative effect on both symptomatic and radiological prognosis. However, all of these patients also had a history of a failed surgery. A history of previous



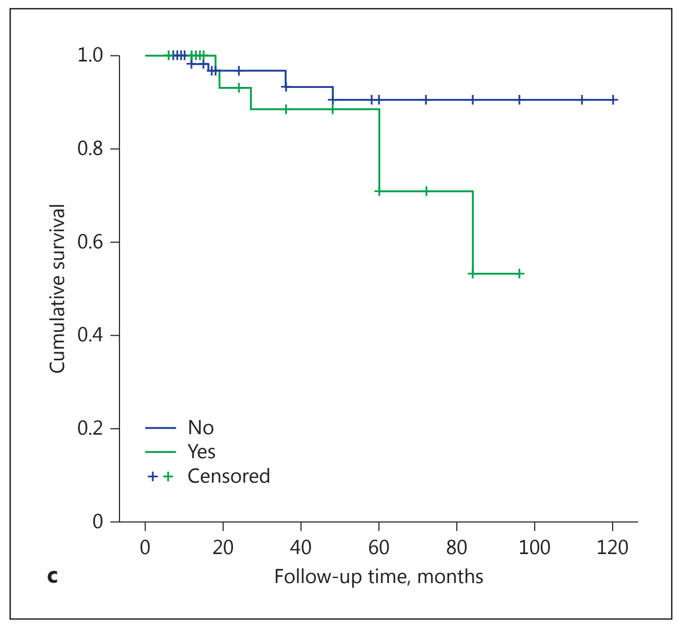


Fig. 1. Kaplan-Meier plot for progression-free survival rates in all patients with cavernous sinus meningiomas (**a**), and patients according to sex (**b**) and previous surgery (primary Gamma Knife radiosurgery [GKRS] and GKRS after previous surgery) (**c**).

surgery was also associated with a worse neurological outcome. Accordingly, Hasegawa et al. [19] proposed that in postsurgical cases, the tumor cannot be confined suitably in the margin dose. Moreover, many symptoms that are present in such patients may be a direct surgical injury and/or postirradiation deficit rather than tumoral infiltration itself. Therefore, GKRS demonstrated limited symptomatic improvement in these patients.

According to our results, patients in whom both a higher tumor coverage and isodose line were achievable, there was a higher probability to reach a radiological improvement. However, the tumor volume negatively affected the radiological outcome. This could be explained by the fact that a complete tumor coverage is more difficult to achieve in larger tumors. Likewise, the presence of trigeminal sensory deficits at presentation negatively affected the radiological prognosis. The reason may be an underlying advanced infiltration of the tumor that makes it more resistant to treatment. The importance of tumor extension, tumor coverage, and marginal dose on out-

Table 6. Comparison of more salient studies on Gamma Knife (GK) radiosurgery of cavernous sinus meningioma

First author/year	Patients *n*	Follow-up, months	Progression-free survival		Radiological response, %		New CND, %	SRS modality
			5 y	10 y	regress.	stable		
Duma [35], 1993	34	26 (median)	n/a		56	44	11.8	GK
Pendl [36], 1998	41	39 (mean)	n/a		34	63		GK
Morita [24], 1999	88	35 (mean)	95		68	29.5	10.2	GK
Liscak [26], 1999	67	19 (median)	n/a		52	48	3.8	GK
Roche [17], 2000	80	30.5 (mean)	92.8		31	64	3	GK
Shin [18], 2001	40	42 (mean)		82.3	37.5	47.5	2.5	GK
Lee [11], 2002	159	35 (mean)	93.1	93.1	34	60	9	GK
Nicolato [28], 2002	156	48.9 (mean)	96.5		69.3	27.2	1	GK
Iwai [9], 2003	42	49.4 (mean)	92		29	64	4.8	GK
Maruyama [27], 2004	40	46 (mean)	94.1		n/a		25	GK
Kuo [25], 2004	57	42 (mean)	97		46	51	2.2	GK
Metellus [12], 2005	36	63.6 (median)	94.4		29–52.7		0	GK
Pollock [16], 2005	49	58 (mean)	80–85		59	41	10	GK
Hasegawa [18], 2007	115	62 (median)	87	73	51	37	12	GK
Kimbal [10], 2009	49	50 (median)	100	98	79	19	3.5	LINAC
Spiegelmann [15], 2010	102	67 (mean)	98		58	40	4	LINAC
Skeie [14], 2010	100	82 (mean)	89.4	83.8	22	62	20	GK
dos Santos [7], 2011	88	86.8 (mean)	92.5	82.5	73.8	15.9	12.5	LINAC
This study	166	32.4/24 (median/mean)	90.1	75.8	57.3	35.5	7.2	GK

CND, cranial nerve deficits; SRS, stereotactic radiosurgery; y, years.

come were also mentioned by Shin et al. [18]. They proposed the marginal dose of 14 Gy to be an important limit: if it could not be achieved, surgical intervention should be recommended. However, considering the marginal dose of 12 Gy, Hasegawa et al. [19] could not find any significant difference in GKRS results. Although there was no significant relationship between the marginal dose or the tumor extension and outcome in our study, the results showed better tumor control with higher tumor coverage rates. As the occlusion of vascular supply to the tumor is the most convincing explanation for the GKRS effect, the complete coverage of the tumor especially at the dural bases (that comprises the vascular supply and is the most important site of tumor recurrence) is vital to achieve tumor control [7, 32]. Among different types of tumor extensions, those tumors that entered the suprasellar compartment had a worse radiological response. One may attribute it to a more conservative dose planning to spare the optic apparatus; however, radiosurgical parameters were not significantly different in this group of patients compared to the others.

The PFS rate in this study is in agreement with those of other studies (summarized in Table 6). It re-insists on the efficacy of GKRS in CSM patients either as a primary or adjunct treatment. There was a trend in patients with higher tumor coverage to have a better PFS rate. However, it may indirectly show more indolent tumors that can be enclosed in a desired radiosurgical field.

It is now clear that curative surgery as the sole treatment is not a secure and sufficient option in many cases of CSM [6]. According to the present literature, primary GKRS is a reasonable, safe, and effective option for these tumors. Since GKRS is effective in other pathologies in this location, such as schwannoma and pituitary adenoma, this modality can be considered as the primary and the sole treatment option in patients suspected to have CSM [19]. The issue that is not clear is how to assign a patient either for primary GKRS or for surgery plus GKRS. Lee et al. [11] proposed that CSM with a diameter <3 cm or a volume <15 cm^3 be considered for primary GKRS. However, they did not explain a strong logic behind it. Hasegawa et al. [19] suggested primary GKRS as an option for small or moderate tumors without specific criteria for patient selection. With the current body of literature, most skull base surgeons would adhere to the conventional and routine idea of performing surgery and reserve GKRS for the presence of remnant tumors or tumor recurrence [2, 5, 7, 20, 21, 33, 34]. Therefore, unfortunately, many patients are deprived of the possible benefits of primary GKRS. According to Shin et al. [18], if a marginal dose of 14 Gy could be achievable, primary GKRS is an option. According to our results, if adequate tumor coverage could be achieved in dose planning (although no significant cutoff point was found), while limiting the radiation dose to the critical structures, GKRS can be considered.

In our study, the complication rate was within the range reported in other studies (Table 6). It shows that GKRS is a relatively safe method. However, significant and even fatal complications like severe radionecrosis, peritumoral edema, and hydrocephalus can occur after GKRS. Symptomatic hypopituitarism as a complication of GKRS was encountered in our patients. However, we did not perform routine pituitary axis tests in follow-up sessions, and this could be a limitation of this study.

Limitations

In patients with no previous surgery, the diagnosis of meningioma is made by radiological features. So, other radiological mimickers of meningioma such as hemangiomas and schwannomas may be present among the patients, and they may have different responses to radiosurgery. New generations of GK systems are now available, and their development in hardware and software may provide better results than what we observed using a model C system. Follow-up time in our study is shorter than in most similar studies, and this may affect the accuracy of the study. The average tumor volume in our study is higher than that in most similar studies, and this may change the effectiveness of GKRS and the complication profile.

Conclusion

This study is the first report on GKRS for CSM in the Middle East. The safety and efficacy of primary or postoperative GKRS in the control of CSM were demonstrated by this study. We also showed a significant effect of tumor volume and tumor coverage on prognosis. Therefore, primary GKRS can be suggested as the sole treatment to be considered for patients in whom an adequate radiosurgical tumor coverage could be achieved. Accordingly, with a correct understanding of benefits and shortcomings of surgical or radiosurgical treatments, a neurosurgeon can choose the best approach for each individual patient. However, larger studies with longer follow-ups and inclusion of quality-of-life assessment may be needed for a stronger recommendation.

Disclosure Statement

The authors have no conflict of interest to disclose.

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