Original Article

Single-Fraction Gamma-Knife Radiosurgery with or without Previous Surgery for Cavernous Sinus Meningiomas: A Single-Center Experience and Systematic Literature Review

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ABSTRACT

Background: The most effective treatment method for meningiomas is surgical treatment. However, complete resection of cavernous sinus meningiomas is quite difficult. The biggest reasons for this are; narrow surgical corridor, the optic chiasm is the close relationship between the cranial nerves and anterior cerebral and internal carotid arteries. Gamma knife radiosurgery (GKRS) may be a good option in these lesions with high mortality and morbidity. **Aim:** This study aimed to evaluate and compare the early effects at a mean of 6 months and 3 years and outcomes between surgery followed by gamma knife radiosurgery (GKRS) and GKRS alone for cavernous sinus meningiomas. **Methods:** We included 20 patients with cavernous sinus meningioma treated via single fraction Leksell Gamma Knife Perfexion (Elekta Instruments; Stockholm, Sweden) between 2015 and 2018. The mean age of the patients was 54.95 (range: 32–77) years. Nine patients underwent primary surgery (for the resection of extracavernous components of the tumor) followed by GKRS (for the resection of intracavernous components of the tumor) (group A). Meanwhile, 11 patients were managed with GKRS alone (group B). The tumor volume ranged from 2.8 to 32.8 (mean: 14.76) cm3 and the isodose to the tumor margin from 10 to 13.5 (mean: 11.65) Gy. **Results:** In total, 20 patients were followed up at a mean time of 18.95 (range: 6–36) months. The mean Karnofsky Performance Score of the patients was 95.2%. The mean follow up times of groups A and B were 23.6 and 15 months, respectively. Meanwhile, only patients with a follow up time of at least 6 months were included in the study. The mean follow up time after GKRS in group A was 17.6 months. There was no change in the tumor volume in 15% of patients. In the remaining cases, the tumor volume decreased. The mean tumor regression rates were 82.2% in Group A and 17.7% in Group B. The tumor volume did not decrease in three patients (n = 1, group A and n = 2, group B). Cranial nerve deficits improved, worsened, and remained stable in 46.6%, 26.6%, and 26.6% of cases, respectively. The temporary morbidity rate was 10%. In group A, transient postoperative diabetes insipidus was observed in one patient and atelectasis in another. None of these complications affected the final status of patients. The mortality rate after treatment was 0%. **Conclusion:** Volume staged GKRS is safe and effective for cavernous sinus meningioma. GKRS is effective for long term tumor growth control and has

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a low complication rate. Hence, it is the preferred management strategy for tumors with a suitable volume (average tumor diameter: 3 cm or volume: 10 cm3). In tumors with a volume of more than 10 mL and/or without a 3 mm safety margin with the optical system, it is recommended to prepare for radiosurgery by cytoreducing the tumor volume surgically. Based on our opinion, the best results were obtained by GKRS to the intracavernous.

Keywords: *Cavernous sinus, gamma-knife, meningioma*

Introduction

Meningiomas (45%) are the most common type of cavernous sinus tumors. They originate from arachnoid cap cells in the arachnoid villi and are located epiarachnoidally, and 90% of them are benign.[1] Moreover, they account for 20% of all brain tumors (13%–26%).[2] Its incidence is 2–6/100,000, and its prevalence is 1%–2% based on autopsy or screening studies.[3] Numerous tumors progress asymptomatically. Stage I benign meningioma is the most common, and the recurrence rate of this type of tumor after radical surgery can vary between 7% and 20%. Stage II atypical meningiomas are only observed in 4.7%–7.2% of patients, with recurrence rates of 29%–40% even if they are completely resected. Stage III anaplastic malignant meningiomas account for 1%–2.8% of all cases. They are also associated with an extremely high rate of recurrence (50%–78%) even after complete resection.[2,3]

There is an ongoing debate about different treatment strategies for cavernous sinus meningiomas. Radical surgical resection is the complete resection of a tumor, including the intracavernous sinus component.[1-3] Conservative surgical resection with radiosurgical treatment involves radiosurgery of the intracavernous sinus portion after resection of extracavernous sinus components. To date, microsurgery and radiosurgery are used as complementary treatments for the management of patients with cavernous sinus meningioma. A few data, which can be used for the direct comparison of outcomes between both approaches used in a single institution, are available.

Surgical management of meningiomas aims to completely resect tumors with dural extension. However, complete resection of cavernous sinus meningiomas is challenging due to the narrow surgical corridor and the close relationship between the tumor and optic nerves, optic chiasm, cranial nerves, and anterior cerebral and internal carotid arteries. Accordingly, the mortality and morbidity rates of surgical treatment in this region are high.[4]

Materials and Methods

This retrospective study included patients with cavernous sinus meningioma treated with Elekta Leksell Perfexion at our GK unit between 2015 and 2018. In total, nine patients underwent radical extracavernous sinus resection following GKRS of the intracavernous part of the meningioma (group A). Meanwhile, 11 patients were managed with GKRS alone (group B). Table 1 depicts the demographic and clinical information of patients.

None of the patients had a previous history of surgery or radiation therapy. Transarterial embolization of the arteries supplying the tumor was not performed on any patient before surgical resection. Comprehensive medical, neurological, neurophysiological, ophthalmological, and neuroradiological evaluations were performed before and after each surgery. During radiosurgery, patients were immobilized in a Leksell stereotactic coordinating frame, and contrast-enhanced magnetic resonance imaging (MRI) was performed to obtain accurate information about the shape, volume, and three-dimensional coordinates of the tumor. Next, single-fraction GKRS was performed [Figure 1].

Neurosurgeons and radiation oncologists performed dose planning using commercially available software (GammaPlan; Elekta Instruments, Stockholm, Sweden). In principle, the dose at the tumor margin was >13 Gy, which is within the 50% isodose range. If the tumor is far enough from the optic apparatus and the brainstem, the dose was occasionally increased based on the tumor volume to improve long-term tumor control [Figure 2].

All patients underwent T1- (gadolinium-enhanced and gadolinium-free) and T2-weighted MRI, and tumor volume was then calculated. Postoperative control MRI was performed at 24–48 h and every 6 months within the first 3 years [Figures 3 and 4].

The extent of surgical resection was determined based on MRI images obtained 24–48 h after surgery and was classified as total (no residual tumor or small area with question marks), subtotal (<97% resection of the mass, presence of significant residual tumor), and partial (<90% resection of the mass). Single-fraction GKRS was applied to group A after 6 months. Surgical complications were defined as clinical deterioration after surgery that occurred during hospitalization. Cranial nerve morbidities and pretreatment, post-treatment, and final Karnofsky Performance Score were evaluated and compared between groups A and B.

Data analysis was performed using the Statistical Package for the Social Sciences software version 25 (IBM Inc.). The normality of values was evaluated using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The homogeneous distribution of variances was examined using Levene's test. Independent Student's *t*-test was used for the cross-group comparison of Mann–Whitney *U* test parameters.

Ethics committee

Due to the nature of this study, the need for ethical approval was waived.

Table 1: Baseline characteristics of 20 patients with cavernous meningiomas

Gender	
Female	14
Male	6
Age (year)	
Mean	54.95
Range	32–77
Karnofsky Performance Score mean (%)	95.2%
Presenting symptoms (*n*)	
Headache	12
Decreased vision	12
3rd nerve involvement	9
n	1
5th nerve involvement	3
6th nerve involvement	2
Tumor volume (cm^3)	
Mean	14.76
Range	2.8–32.8
Tumor regression mean (%)	
Post GKRS	17.7
Post-surgical + GKRS	82.2
Follow-up (months)	
Mean	18.95
Range	6–36

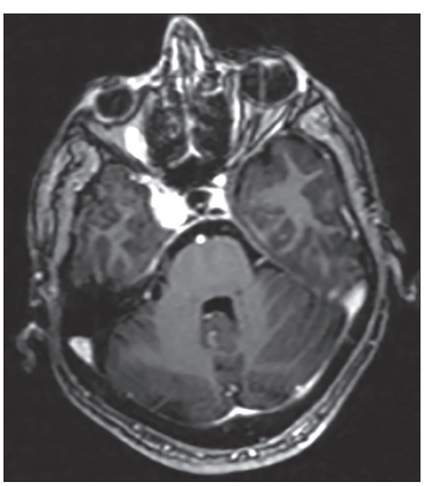

Figure 1: Contrast-enhanced T1WI image before gamma-knife treatment

Results

There were no disease-related mortality or surgical complication during follow-up. The histological diagnoses were papillary meningioma (*n* = 2), chordoid meningioma (*n* = 1), and fibrous meningioma (*n* = 3). The mean follow-up times of groups A and B were 23.6 and 15 months, respectively. Only patients with a follow-up of at least 6 months were included in the study. Seven patients in group A and eight in group B had cranial nerve deficits before treatment. Moreover, the deficits improved, worsened, and remained stable in 46.6%, 26.6%, and 26.6% of cases, respectively. The temporary morbidity rate was 10%. In group A, we identified transient postoperative diabetes insipidus in one patient and atelectasis in another. None of these complications were found to affect the final status of the patients. The overall permanent morbidity rate was 20%. Table 2 shows the neurological findings.

Neurological outcomes and complications

Group A

Table 3 shows the volumetric analysis results of group A. After a significant volumetric decrease in the early postoperative period, in the 6th month, a control MRI was performed to assess residual intracavernous tumor volume, and patients then received single-fraction GKRS. The mean follow-up time after GKRS was 17.6 months. The mean decrease in tumor volume after GKRS was 22.6%, and the overall regression was 82.2%. In one patient, the tumor volume remained stable after GKRS. We identified transient postoperative diabetes insipidus in one patient and atelectasis in another. The mortality rate after treatment was 0% [Table 3].

Group B

Table 4 shows the tumor volumetric analysis results of

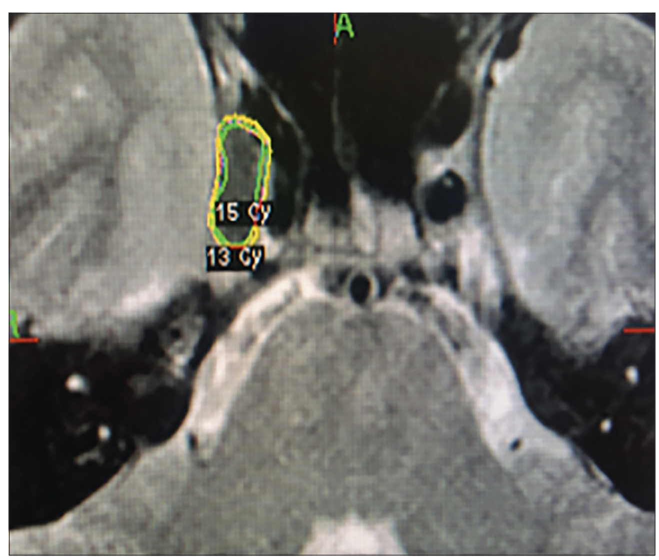

Figure 2: Gamma-knife, preoperative calculation

group B. Unlike in group A, there was no significant decrease in tumor volume in the early postoperative period. Then, a slow decrease was observed after GKRS. The mean follow-up time was 15 months after GKRS. The mean decrease in the percentage of tumor volume was 17.7%. In two patients, the tumor volume remained stable. None of the complications were found to affect the final status of the patients. The mortality rate after treatment was 0% [Table 4].

According to the statistical analysis, groups A and B were comparable and homogeneous (Levene's

Table 2: Neurological outcomes and complications

	Post-GKRS (*n*)	Post-surgical (*n*)	Post-surgical + GKRS (*n*)
Cranial nerve deficit	2	1	1
Improved	None	None	None
Stable	1	None	1
Worsened	1	1	None
New deficit	None	None	None
Oculomotor palsy	4	5	2
Improved	1	3	None
Stable	3	None	2
Worsened	None	2	None
Trigeminal dysfunction	2	1	0
Improved	2	1	None
Stable	None	None	None
Worsened	None	None	None
Follow-up	11	9	9
Mean (months)	15	23.6	17.6

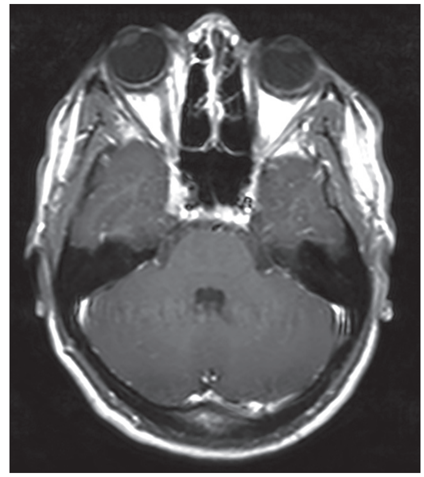

Figure 3: Contrast-enhanced T1-weighted image, 1st-year control

Table 3: Predictors of tumor regression and time-to-regression for cavernous sinus meningiomas in Group A

Patient	Age	Gender	Tumor volume at surgery (cm^3)	Tumor volume at GKRS (cm^3)	Prescription isodose (Gy) Tumor volume 50%	Interval between treatment to last follow-up (months)	Interval between GKRS to last follow-up (months)	Tumor volume at the last follow-up (cm^3)	Tumor regression after GKRS (%)	Total tumor regression (%)
1	62	Male	17.8	3.56	10	28	22	2.9	18.6	83.8
2	47	Female	23.2	5.8	11	18	12	4.7	19.0	79.8
3	55	Female	30.3	8.48	13	36	30	6.2	27.0	79.5
4	58	Male	15.7	3.29	10	25	19	2.32	29.5	85.3
5	64	Female	32.8	8.52	13.5	22	17	7.3	14.4	77.8
6	57	Female	28.6	5.14	11	32	25	3.4	34.0	88.2
7	60	Male	24.3	5.3	11	20	14	3.2	39.7	86.3
8	48	Female	19.8	4.7	10	17	11	3.7	21.2	81.3
9	44	Female	29.70	6.5	13	15	9	6.5	0.00	78.1

Table 4: Predictors of tumor regression and time-to-regression for cavernous sinus meningiomas in Group B

Patient	Age	Gender	Tumor volume at GKRS (cm^3)	Prescription isodose (Gy) tumor volume 50%	Interval between treatment to last follow-up (months)	Tumor volume at the last follow-up (cm^3)	Tumor regression (%)
1	52	Female	2.8	10	7	2.8	0.00
2	32	Female	7.3	13	12	5.3	27.40
3	67	Male	6.4	12	32	3.0	53.10
4	43	Female	5.3	11	6	5.3	0.00
5	50	Female	7.0	12	11	6.5	7.14
6	54	Female	5.5	11	10	5.0	9.09
7	38	Female	3.7	10	30	2.2	40.50
8	63	Female	5.9	11	9	5.5	6.77
9	72	Female	14.2	14	12	13	8.45
10	77	Male	8.7	13.5	24	6.7	22.90
11	56	Male	6.2	12	13	5	19.35

Table 5: Description of all reviewed studies for each treatment modality, excluding Linac RS, fractioned and hypofractionated RS treatment series

Author	Patients (*n*)	Receiving surgical treatment (%)	Tumor volume (cm^3)	Follow-up time (months)	Clinical improvement (%)	Radiological tumor regression (%)	PFS at 5 year (%)
Duma *et al*., 1993[18]	34	82	5.2	26	24	56	N/A
Liscak *et al*., 1999[6]	67	36	7.8	19	36	52	N/A
Roche *et al*., 2000[16]	80	37.5	5.8	30.5	N/A	31	92.5
Kobayashi *et al*., 2001[19]	27	63	N/A	20.2	N/A	N/A	N/A
Shin *et al*., 2001[20]	40	70	4.3	42	24	N/A	86.4
Iwai *et al*., 2003[21]	42	52	14.7	49.4	28.6	59.5	92
Nicolato *et al*., 2002[17]	156	52	8.3	48.9	78.5	61.5	96.5
Lee *et al*., 2002[7]	159	49	6.5	39	29	34	93.1
Kuo *et al*., 2004[22]	57	7	3.4	15.2	28	46	N/A
Maruyama *et al*., 2004[8]	40	57.5	5.4	47	20	N/A	94.1
Pollock and Stafford, 2005[23]	49	0	10.2	58	26	N/A	82.5
Liu *et al*., 2005[24]	88	N/A	6.6	32.5	N/A	43.5	94
Metellus *et al*., 2005[9]	74	N/A	5.2	63.6	53.8	52.7	94.4
Hasegawa *et al*., 2007[11]	115	57	14	62	64	N/A	87
Franzin *et al*., 2007[25]	123	33	8	36	23	43.1	90.5
Malik *et al*., 2009[12]	101	0	N/A	44	N/A	N/A	87
Skeie *et al*., 2009[26]	100	60	7.4	82	21	22	89.4
Zada *et al*., 2010[27]	59	N/A	6.5	75	N/A	N/A	N/A
Williams *et al*., 2011[28]	138	61	7.5	84	N/A	48	95.4
Hayashi *et al*., 2012[29]	19	26	N/A	55	N/A	68	N/A
Zeiler *et al*., 2012[30]	30	40	7.9	36.1	N/A	34.6	N/A
Kano *et al*., 2013[13]	272	36	7.9	62	31	60	94
Pollock *et al*., 2013[14]	115	40	9.3	89	41	N/A	N/A
Hafez *et al*., 2015[15]	62	18	5.7	36	N/A	19	95

Figure 4: Contrast-enhanced T1-weighted image, 2nd-year control

test). Moreover, they significantly differed in terms of total tumor regression rates ($P < 0.001$, Mann–Whitney *U* test). However, there was no significant difference in terms of tumor regression rates after GKRS ($P > 0.05$).

In our study, the best results were obtained by GKRS to the intracavernous part after surgical resection of extracavernous components of the tumor. In our opinion, the gold keyword was here cytoreduction of the tumor volume.

Discussion

To date, cavernous sinus meningiomas are resected with conventional, well-defined skull base approaches.[5] Radiosurgery is another modality used in the treatment of these tumors.[6-9] In this study, we compared the efficacy of surgery + gamma-knife and gamma-knife alone for cavernous sinus meningiomas. A surgical oncological cure is difficult to achieve due to the anatomical localization and invasive nature of cavernous sinus meningiomas. Cavernous sinus meningiomas are intradural tumors.[1,2] According to the grading system described by DeMonte *et al*.,[5] the extent of cavernous sinus meningioma resection is not better than that of grade 4a, as it exhibits a certain degree of infiltration into the anatomical structures and bone tissues in the cavernous sinus. This implies the need for deliberate subtotal resection of the tumor and complete microscopic resection of tumor dural adhesion to protect the cranial nerves or blood vessels. The degree of internal carotid artery (ICA) involvement and vascular wall invasion by the meningioma that covers the ICA is another determinant of oncological complete resection.[10] ICA and cavernous branch resection partially devascularizes the cranial nerves of the cavernous sinus. Moreover, it may decrease functional recovery rates, resulting in nerve infarction.[10] In terms of anatomical structure, the absence of arachnoid surfaces is another cause why oncological eradication of these tumors cannot be achieved.

Postoperative MRI could help accurately determine residual tumor volume within 24–48 h, and this is a valuable tool in deciding the next treatment step. MRI performed within 24–48 h after surgery can determine the exact volume of residual tumor and the next treatment step on time. Commonly, the outcome is cytoreduction of the extracavernous tumor, which can protect brain function, and another strategy is used to confine the tumor within the cavernous sinus to preserve cranial nerve functions. In our field, an understanding of the nature of surgical treatment for these tumors has made us consider that pursuing the goal of radical excision via surgical procedures using modern skull base techniques (group A) is often unnecessary as they can lead to complications and decrease the quality of life. These complications can be prevented with a more conservative strategy (group B). Nevertheless, cranial nerve paralysis after surgical excision of the intracavernous compartment of the tumor is the greatest concern. Previous studies reported that the incidence rates of permanent morbidity range from 10% to 59%, and the cranial nerves are frequently involved.[2] In this study, the rate of extraocular deterioration is determined mainly based on the aggressiveness of the surgical strategy. Hence, based on our experience, complications including hemiparesis were more likely to be associated with the extracavernous spread of the tumor. Extraocular nerve palsy is the most common complication encountered during tumor management. This neurological finding is usually reversible within 6 months. However, it commonly occurs, and it is extremely disturbing that it becomes the main determining factor for the quality of life in the postoperative period. The probability of recovery from extraocular palsy after surgery is higher with GK treatment of the intracavernous compartment (group B). Moreover, a postoperative manifestation of extraocular nerve palsy is more common in the radical resection group (group A). Preoperative detection of extraocular palsy is not an indication of radical surgery. However, this does not apply to the optic nerve. Preoperative optic nerve dysfunction should be managed via the surgical resection of the part compressing the extracavernous tumor. Therefore, preservation of the normal optic nerve function or reduction in the incidence of meningioma that is far from the optic system may be an indication for surgery in preparation for radiosurgery. Although radiosurgery cannot eradicate neoplasms, it improves their natural development and helps facilitates clinical recovery or symptom stabilization. The current and recent studies showed that radiosurgery is effective in selected cases of cavernous sinus meningioma. The tumor growth control rate of cavernous sinus meningiomas after radiosurgery is >90%.[11-15] In the literature, volume reduction has been observed in 31% of cases in a large series.[16] In another study, the rate was 61.5%.[17] From a clinical perspective, all published series showed that >90% of participants had stable or improved neurological conditions. Moreover, radiosurgery can improve progression-free survival (PFS) [Table 5].[6-9,11-14,18-30]

In the study by De Jesús *et al*., the 5-year PFS rate after radical microsurgery resection was 62%.[1] By contrast, in several radiosurgery series, the 5-year rate PFS rate ranged from 85.7% to 95.5%. The tumor volumes in most microsurgery series are commonly larger than those in radiosurgery series. Hence, based on the current and previous studies, radiosurgery cannot be the primary treatment method for cavernous sinus meningiomas. Rather, it can be considered for meningiomas with a volume of <10 mL. Radiation sensitivity of the optical apparatus is an issue, limiting the use of radiosurgery for the management of cavernous sinus meningiomas. Duma *et al*.[18] showed that 2 of 34 patients had radiation-induced neuropathy after radiosurgery. In our practice, we concluded that there should be a difference of at least 3 mm between the closest optic anatomical structure and the tumor border. Otherwise, as mentioned earlier, the initial cytoreduction of meningioma far from the optical system is essential.

Conclusions

Age is not a common parameter in decision-making among patients whose systemic condition is suitable for surgical intervention. However, some authors recommend surgery as the first-line treatment among young patients. In symptoms requiring surgical treatment including optic nerve compression and extraocular nerve paralysis, clinical reduction of diplopia can be considered after radiosurgery.

Clinical or radiological findings including optical system compression can be used as a basis for treatment decision-making. A distance of at least 3 mm between the tumor and the optical anatomical structures is required for the safe and effective radiosurgical treatment of cavernous sinus meningiomas. In tumors with a volume of more than 10 mL and/or without a 3 mm safety margin with the optical system, it is recommended to prepare for radiosurgery by cytoreducing the tumor volume surgically.

Contrast-enhanced MRI should be performed within 24–48 h after surgery to prevent confusion in obtaining a differential diagnosis because of the appearance of metabolites caused by postoperative inflammation and hematoma resolution.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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