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Clinical Experiences Using CyberKnife for Large-Volume Meningiomas: A Preliminary Study

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Background This preliminary study evaluates the safety and efficacy of CyberKnife radiosurgery (CKRS) for large-volume meningiomas (≥10 cm^3), where surgical options may be limited due to tumor location or patient health conditions.

Methods We retrospectively analyzed 18 patients with meningiomas treated with CKRS at Gyeongsang National University Hospital between 2010 and 2020. Tumor control and survival rates were evaluated, with follow-up imaging performed regularly.

Results CKRS achieved a 5-year overall survival rate of 92.3% and a 5-year tumor control rate of 93.8%. Symptomatic peritumoral edema occurred in 61.1% of patients, with 16.7% requiring surgical intervention.

Conclusion CKRS appears to be a promising option for patients with large meningiomas, showing good tumor control and manageable complications. Further studies with larger cohorts are necessary to confirm these findings.

Keywords CyberKnife; Hypofractionated radiosurgery; Meningioma; Tumor control; Outcome.

INTRODUCTION

Meningiomas are the most common primary intracranial tumors [1]. Surgical resection is the preferred treatment for accessible meningiomas, but radiosurgery is used for lesions in critical locations, especially for small- to medium-sized tumors. However, the application of radiosurgery to large-volume meningiomas (≥10 cm^3) remains controversial due to the potential for treatment-related toxicity. However, for patients without other clinical alternatives, it is necessary to validate whether radiosurgery is worth attempting as an alternative therapeutic option, and previous reports suggest its potential as an alternative treatment method [2-4].

This study aims to assess the clinical outcomes of CyberKnife hypofractionated radiosurgery for large meningiomas to determine its feasibility as a treatment option.

MATERIALS AND METHODS

Study design and patient selection

This retrospective study was conducted at the CyberKnife Center of our institute from 2010 to 2020. The primary objective was to evaluate the effectiveness and safety of CyberKnife hypofractionated radiosurgery for patients with large-volume meningiomas. Patients were eligible for inclusion if they had a diagnosed large-volume meningioma, defined as a target tumor volume of 10 cm^3 or more, and had received CyberKnife radiosurgery (CKRS) as their primary therapy at our center. Additionally, patients were required to have a follow-up period of at least 2 months to ensure sufficient post-treatment data for accurate outcome assessment. Exclusion criteria included tumors smaller than 10 cm^3, previous craniotomy for meningioma, and follow-up loss or insufficient observation period (less than 2 months).

In follow-up radiological evaluations, tumor volume measurements were calculated by manually drawing the area of the region of interest (ROI) on each cross-sectional plane of the available contrast-enhanced T1-weighted image (T1WI)

of MRI scans and accumulating the sum of the product of the slice thickness and the ROI area. If there were any possible axial, sagittal, and coronal series of T1WI contrast enhancement images, each was calculated separately, and the average of the volumes calculated from each of these was taken. Each measurement was performed three times by the author and the mean value was obtained. If MRI T1 contrast-enhanced images are unavailable, the volume was calculated through the tumor margins differentiated by density on precontrast CT. When contrast enhancement series were available, the volume was estimated through the enhanced tumor silhouette.

We collected all of the patient data based on information contained in hospital electronic medical records and followed the case record form, which was approved by the institutional review board (IRB). As a retrospective study, there was no risk to the subjects, and the IRB of Gyeongsang National University Changwon Hospital approved (GNUH 2024-08-010) the exemption of consent from the subjects.

Treatment protocol

All patients underwent radiosurgery using CyberKnife (Accuray Inc., Sunnyvale, CA, USA). For treatment planning, patients received contrast-enhanced MRI and CT scans prior to radiosurgery. Each scan obtained high-resolution slices (2.5 mm for MRI T1 contrast enhancement and 1.3 mm for CT), and fusion imaging was used to determine the treatment scope of the target tumor. Fractionation of each session in the radiosurgery was performed at daily intervals.

During each treatment session, patients were admitted and received radiosurgery, with intravenous dexamethasone 5 mg administered every 6 hours from the day of treatment until the day of the last fractionated radiation exposure. An antacid was used concurrently for gastric protection. Patients were discharged on the day they received the last fractionated exposure. The discharge prescription involved initiating treatment with methylprednisolone 20 mg, tapering every 2 days over a period of 10 days. Two weeks post-discharge, patients were followed up in the outpatient setting to assess their clinical course and adverse effect, and regular radiological monitoring was continued.

Follow-up and monitoring

After the initial treatment, patients underwent a rigorous follow-up schedule to monitor treatment outcomes and detect any potential complications early. MRI was conducted at 3 months, 6 months, and 12 months following the CKRS, with subsequent MRIs performed annually. In cases where additional assessment was needed, CT scans were performed. The follow-up imaging studies were crucial for evaluating the primary endpoints of the study, which included local tumor control and overall survival rates, as well as identifying and managing any adverse effects or complications arising from the treatment.

Follow-up CT or MRI were also used to evaluate peritumoral edema. The edema was graded based on its extent: grade 0 for no edema, grade 1 for less than 25% of the tumor's maximum diameter, grade 2 for 25% to 75%, and grade 3 for more than 75%.

Data collection and analysis

Patient demographics, tumor characteristics, treatment details, and follow-up data were meticulously collected and analyzed. The primary outcomes assessed were local tumor control and overall survival rates. Secondary outcomes included the incidence and management of treatment-related complications, particularly symptomatic peritumoral edema. The collected data were subjected to statistical analysis to determine the efficacy and safety of the CKRS in the study population. Survival analysis was performed using the Kaplan-Meier method.

RESULTS

Patient demographics

Despite having meningiomas larger than 3 cm, the subjects received CKRS for the following reasons: underlying medical conditions, advanced age, unavoidable use of medications with a risk of bleeding, and refusal of surgical treatment.

Eighteen patients (13 females, 5 males) with a median age of 77.5 years (range 45–90) were included. The median follow-up duration was 30.5 months (range 2–107 months), and the median tumor volume was 14.8 cm^3 (range 11.0–28.6 cm^3). The patients received a median prescription dose of 2,400 cGy (range, 2,100–3,000 cGy) administered in 3 fractions (range, 3–5). The median isodose line was 80%, and the range was 72%–85%.

The most common origin of the tumors was the falx cerebri, accounting for four cases (22.2%), followed by three cases each at the convexity and clinoid. Details are described in Table 1.

Tumor control

The overall local tumor control rate was 94.4% (17/18 patients) with both 1-year and 5-year progression-free survival rates being 93.8% (Fig. 1A). The average progression-free survival was 100.7 months (95% CI 88.7–112.7).

The overall survival (OS) rate for patients who underwent CKRS was 94.4% (7/18 patients). According to Kaplan-Meier analysis, the average survival duration was 100.2 months (95% CI 87.3–113.0), with 1-year and 5-year OS rates of 100% and

Table 1. Characteristics of the patients received CyberKnife radiosurgery

Characteristic	Value (n=18)
Sex	
Male	5 (27.8)
Female	13 (72.2)
Age (yr)	77.5 (45–90)
Follow-up (month)	30.5 (2–107)
Target volume (cm^3)	14.8 (11.0–28.6)
Prescription dose (cGy)	2,400 [2,100–3,000]; mode: 2,400
Isodose line (%)	80.0 [72–85]; mode: 80
Maximal dose (cGy)	3,019.0 [2,824–3,750]; mode: 3,000
Fraction	3 [3–5]; mode: 3
Pretreatment PTE present	5 (27.8)
Tumor location	
Falx cerebri	4 (22.2)
Clinoid	3 (16.7)
Convexity	3 (16.7)
Cerebellopontine	2 (11.1)
Sphenoid	2 (11.1)
Cavernous sinus	1 (5.6)
Olfactory groove	1 (5.6)
Parasagittal	1 (5.6)
Tentorial	1 (5.6)
Previous clinical symptoms	
No deficits	16 (88.9)
Asymptomatic	5
Headache	9
(and/or) Nausea/vomiting	1
(and/or) Dizziness	4
Neurological deficits	2 (11.1)
Hemiparesis	2

Values are presented as n (%) or median [interquartile range] unless otherwise noticed. PTE, peritumoral edema

92.3%, respectively (Fig. 1B). One patient with a history of angina died of cardiac arrest 2 hours after undergoing rescue craniotomy for signs of elevated intracranial pressure that was not controlled by medication after CKRS.

The median maximum volume reduction ratio for the initial gross tumor volume (GTV) was 20.5%, and the median time to achieve this maximum volume reduction was 3.7 months (range, 1.4–58 months) (Fig. 2). General outcomes are described in Table 2.

Adverse events

A total of 16 patients (88.9%) experienced clinical adverse reactions (Table 2). This group included patients with and without cerebral edema as confirmed by follow-up imaging studies. Six of these patients reported transient symptoms of meningeal irritation, such as headaches, dizziness, nausea, and vomiting, which were resolved with symptomatic treatment. Ten of the 16 patients experienced temporary or permanent neurological complications. These complications included progressive or newly onset hemiparesis, sensory changes, visual disturbances, delirium, fatigue, alopecia, resting tremor, and seizures.

Symptomatic peritumoral edema occurred in 66.7% (12/18) of patients, with a median onset of 5.3 months (range, 2.4–13.1 months) (Table 3). After CKRS, the peritumoral edema mostly responded to conservative pharmacological treatments such as steroids and mannitol and resolved without permanent neurological deficits. However, tumor removal surgery was unavoidable in three patients (Table 4). In two of these patients, although no tumor growth was observed, they exhibited progressive neurological symptoms such as unilateral paralysis and dysarthria that did not improve with pharmacological treatment, necessitating rescue craniotomy, and tumor resection. The other patient underwent surgical removal due to tumor growth, progressive right-sided hemiparesis, and signs of increased intracranial pressure such as intractable nausea and vomiting that could not be controlled with conservative pharmacological treatment.

Illustrative cases

Case 1

A 37-year-old female patient with no underlying diseases was referred to the emergency room complaining of headaches and vomiting. A 3.6-cm heterogeneously enhancing mass, suspected to be a left convexity meningioma, was identified on a performed brain MRI scan (Fig. 3). Surgical treatment was recommended, but the patient had a history of fainting during a previous vascular injection and was diagnosed with a cluster B personality disorder; she refused surgical treatment. Considering the patient's life expectancy and tumor size, CKRS was alternatively recommended, and the patient agreed to proceed with it. The gross tumor volume was 19.6 cm^3, and CKRS was performed over three fractions with a prescribed dose of 2,400 cGy at the 80% isodose line.

Seven weeks post-treatment, the patient complained of a dysesthesia sensation in hand opposite the lesion and transient abnormal sensations on half of the face and lips. Still, no brain edema was observed on the follow-up CT. She was administered intravenous dexamethasone 5 mg at 6-hour intervals for 3 days and improved subsequently, leading to her discharge. She was also admitted 14 weeks post-CKRS with the same symptoms and improved with conservative treatment over 3 days, leading to discharge. Six months post-CKRS, grade 1 PTE was the highest level of edema observed in this patient's tumor. Throughout the course, no irreversible neurological

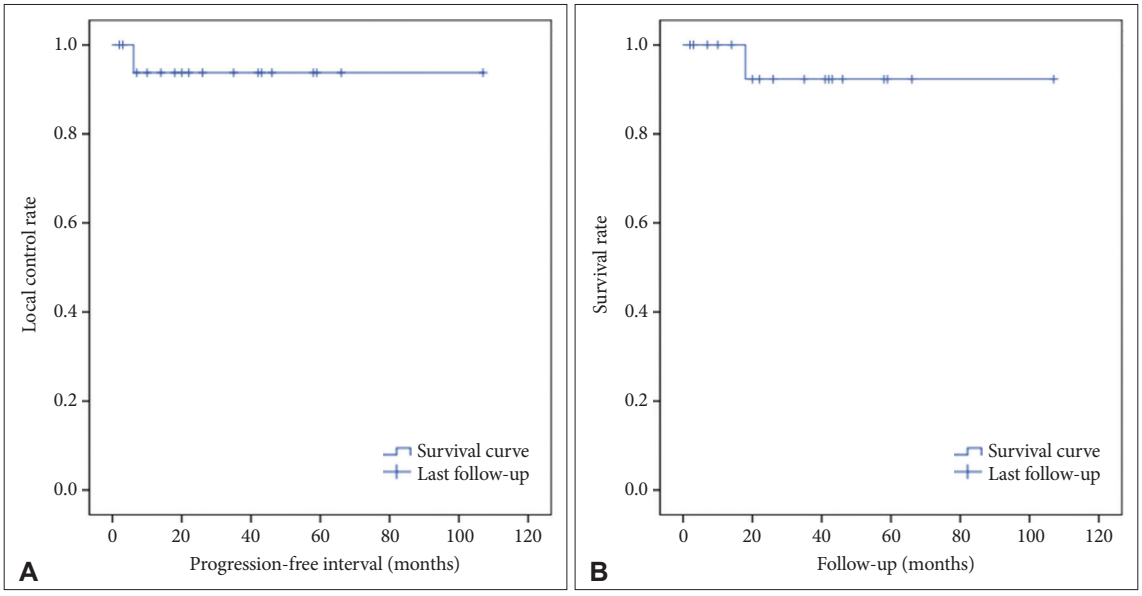

Fig. 1. Local tumor control (A) and overall survival rate (B) over time. A: Mean tumor progression-free day was 100.7±6.1 month (95% CI 88.7–112.7), and 5-year survival rate is 93.8%. B: Mean survival time was 100.2±6.6 months (95% CI 87.3–113.0) and 5-year survival rate was 92.3%.

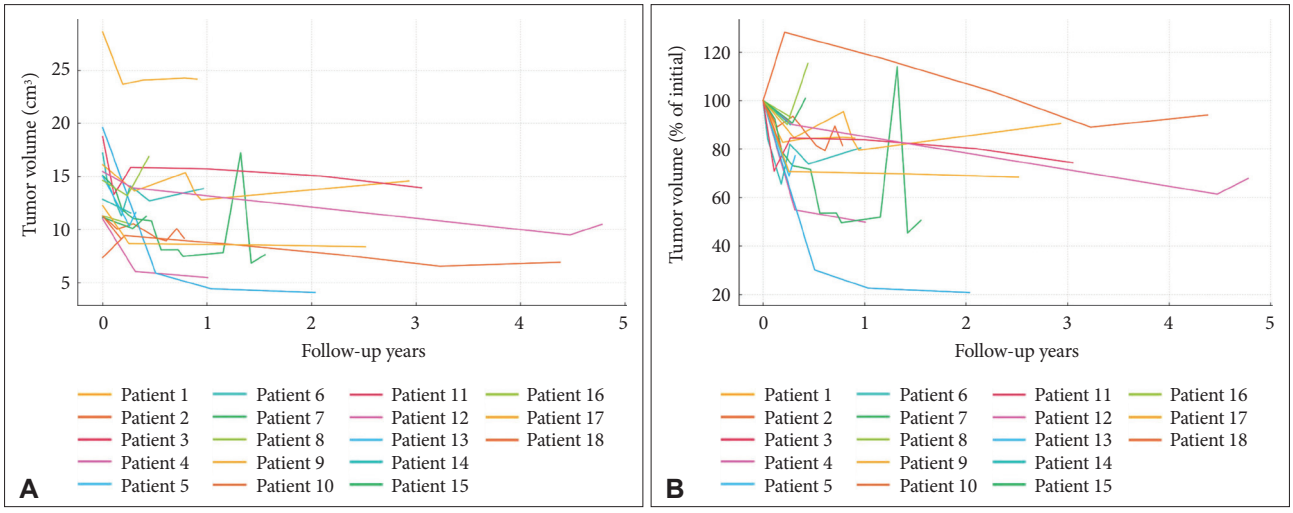

Fig. 2. Changes in tumor volume (A) and volume percentage (B) over follow-up time for all patients.

deficits were noted, and at the last follow-up imaging conducted at 26.5 months, the estimated tumor volume was 4.1 cm^3, which is 20.9% of the original tumor volume (Fig. 3).

Case 2

A 74-year-old female patient presented to the emergency room with decreased consciousness. A CT angiography revealed subarachnoid hemorrhage caused by a ruptured aneurysm in the left posterior communicating artery. Additionally, a 2.5 cm-sized meningioma was discovered in the right cerebellopontine angle. Coil embolization and stent insertion were performed to treat the ruptured aneurysm, and the patient was maintained on aspirin and clopidogrel. Since the meningioma was not causing any neurological symptoms, it was managed with routine follow-up visits without surgical intervention. However, over the course of 2 years and 6 months, follow-up imaging revealed that the meningioma had progressively grown to 3.5 cm. Given the patient's advanced age, ongoing anticoagulation therapy, and a history of acute infarction following the discontinuation of anticoagulation during a prior knee surgery, the risks associated with general anesthesia for tumor removal were considered high. Therefore, CKRS was selected. The estimated volume from the simulation images for CyberKnife increased further to 14.6 cm^3. The CKRS was administered in three fractions, with a prescribed dose of 2,400 cGy at the 78% isodose line. Approximately 160 days after

Table 2. General results after CKRS

Outcomes	Value (n=18)
Overall local control	17 (94.4)
Overall survival	17 (94.4)
Post-CKRS PTE	12 (66.7)
Post-CKRS grade	
1	2 (11.1)
2	1 (5.6)
3	9 (50)
Post-CKRS interval (months)	4.2 (2.4–13.1)
Adverse radiation effect	16 (88.9)
Symptomatic PTE	12
Headache	6
Dizziness	4
Weakness	3
Sensory changes	3
Nausea	2
Weakness	3
Sensory changes	3
Visual symptoms	2
Vomiting	1
Dysarthria	1
Fatigue	1
Delirium	1
Seizure	1
Alopecia	1
Craniotomy after CKRS	3 (16.7)

CKRS, CyberKnife radiosurgery; PTE, peritumoral edema

Table 3. Peritumoral edema after Cyberknife radiosurgery

	Present	Interval (mo.)	Remark
PTE	12/18 (66.7)	5.3 (2.4–13.1)	
PTE location			
Falx cerebri	3/4 (75)	13.1	
Clinoid	1/3 (33.3)	3.3	
Convexity	3/3 (100)	2.4, 4.5	
Cerebellopontine	1/2 (50)	5.8	
Sphenoid	1/2 (50)	3.7	
Cavernous sinus	0/1 (0)	-	No PTE
Olfactory groove	1/1 (100)	-	Previously
Parasagittal	1/1 (100)	5.4	
Tentorial	1/1 (100)	4	

PTE, peritumoral edema

Table 4. Characteristics of patients undergoing craniotomy after CKRS (n=3)

No.	Sex/ age	GTV (cm^3)	Dose (cGy)/Fr.	Location	Rationale	Interval* (mo)
1	F/79	15.1	2,400/3	Convexity	Edema	18
2	F/61	11.1	2,400/3	Parasagittal	Edema	5
3	F/77	14.6	2,400/3	CPA	PD	5

*CKRS to craniotomy interval. CKRS, CyberKnife radiosurgery; GTV, gross tumor volume; FR, fractions; CPA, cerebellopontine angle; PD, progressive disease

treatment, the patient returned to the emergency room due to persistent headaches, nausea, and vomiting. Brain MRI revealed an increase in tumor volume to 16.8 cm^3, along with grade 3 peritumoral edema. The patient was admitted and received conservative management, including 100 mL of 20% mannitol every 4 hours and 5 mg of dexamethasone intravenously every 6 hours. Despite this treatment, her symptoms did not improve, and signs of elevated intracranial pressure progressively worsened. On the 10th day of hospitalization, the patient underwent a craniotomy and tumor removal. Following surgery, her symptoms improved, and she was subsequently discharged. At her last follow-up, 35 months post-surgery, imaging revealed no signs of recurrence (Fig. 4).

DISCUSSION

Since this study is preliminary, caution is needed in interpreting its statistical significance. The results of this study can be used as references in the methodology of subsequent studies to obtain more refined and meaningful. Surgical removal is the primary treatment for symptomatic large volume meningiomas. However, if a patient's general medical condition does not tolerate general anesthesia, an alternative to craniotomy for tumor removal is needed. In our study of 18 patients with large-volume meningiomas, a prescribed dose of 24 Gy was delivered in three fractions, resulting in a 3-year local control rate of 97.4% and a permanent adverse effect rate of 16.7%. These results are comparable to those reported in other similar studies.

It has been reported in previous studies that larger tumor volume is associated with a poorer local control rate [5]. Fatima et al. [3] reported on the outcomes of radiosurgery for 74 large-volume benign tumors. Radiosurgery was performed on lesions with a median volume of 16.0 cm^3 (range, 10.1–65.5 cm^3) using a median dose of 24 Gy (range, 14–40 Gy). They observed a 5-year local control rate of 91.7% and an adverse event rate of 13.5%. Additionally, studies have shown that fractionated stereotactic radiosurgery (FSRS) results in a significantly higher local control rate and greater tumor volume reduction compared to single-session stereotactic radiosurgery (SRS), suggesting that FSRS may be a valuable treatment option for larger meningiomas. However, there is a lack of research on whether more than five fractions lead to better local control rates. Furthermore, no significant differences in local control rates have been observed between FSRS, traditional radiotherapy, and fractionated external beam radiotherapy [6].

More hypofractionated radiosurgery may be associated with

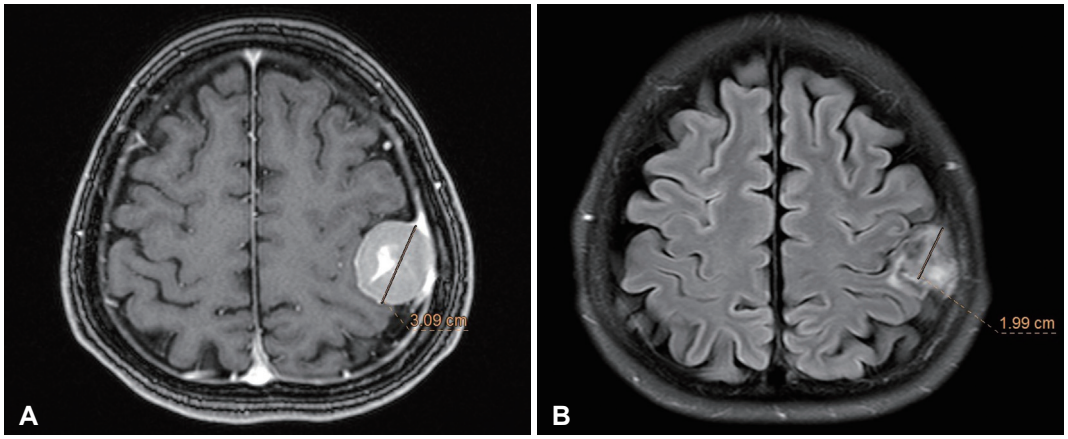

Fig. 3. Initial MRI T1 contrast enhancement image of a 37-year-old woman complaining of nausea and vomiting shows a 19.6 cm^3 meningioma in the left frontoparietal convexity (A). At 26.5 months after CyberKnife radiosurgery, the volume had decreased to 4.1 cm^3 on the last MRI (B).

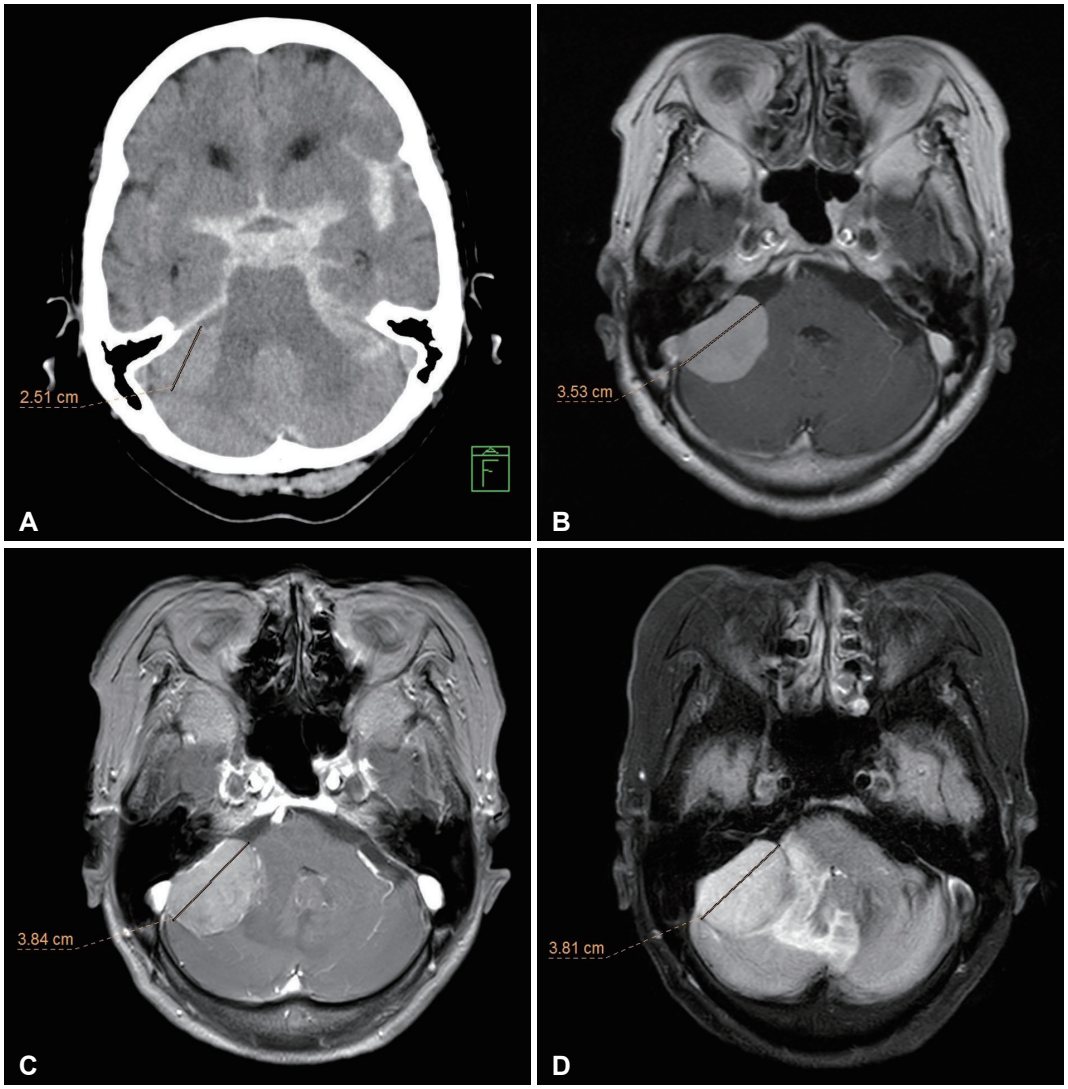

Fig. 4. Initial CT angiography of a 74-year-old woman presented with decreased consciousness showing a 2.5-cm meningioma arising from the right cerebellopontine angle (A). During follow-up, 2 years and 6 months later, growth of the tumor to 3.5 cm (B). At 160 days after CyberKnife radiosurgery, the tumor size had increased to 3.8 cm (C) with symptomatic surrounding edema was observed (D).

lower toxicity. A prospective study using a prescribed dose of 25 Gy delivered in five fractions reported a 5-year local control rate of 97% and an adverse effect rate of 12.7% [4]. There have been reports indicating that single-fraction SRS is associated with a higher incidence of adverse effects, including edema, compared to multi-fraction SRS administered in five or fewer fractions [7].

In the cases included in this study, tumor volume fluctuations were observed, with temporary increases followed by subsequent decreases. Previous studies have reported that intratumoral necrosis (ITN) occurred in 26.8% of patients after gamma knife radiosurgery for meningioma, with 24.5% of these patients experiencing an increase in tumor volume [8]. The increase in tumor volume due to ITN is considered pseudoprogression, and immediate surgery is often unnecessary, as it can usually be managed with conservative treatments such as mannitol and steroids, of which, in most cases, the tumor volume decreases after treatment [8]. Risk factors for the development of ITN include a preoperative tumor volume greater than 3 cm^3, the presence of meningeal enhancement, and having more than 1 cm^3 of tumor volume receiving 70% of the maximal dose [8].

This study has a small number of subjects and a relatively short follow-up period. Caution is required when statistically interpreting patient prognosis and survival. Additionally, the quality consistency of follow-up imaging studies was often not maintained during the follow-up period. Some patients missed scheduled outpatient appointments or underwent follow-up MRIs at different medical institutions. Furthermore, the slices of follow-up CT or MRI scans were not always consistent, which could lead to errors in volumetric measurements.

Nevertheless, this study provides methodological suggestions for investigating the risk factors and frequency of adverse effects in patients for whom radiosurgery is unavoidable, despite the small sample size. Further research is needed on the correlation and timing of known edema risk factors prior to radiosurgery, including tumor location (falx, parasagittal, etc.), predisposing edema, volume (or maximal diameter), and contact surface area [9]. Additionally, it is believed that the fractionated dose and the number of fractions are associated with reduced toxicity, necessitating prospective studies on this matter [4].

In conclusion, CKRS appears to be a worth considering treatment for large meningiomas, achieving substantial tumor control and survival rates with manageable adverse effects. Further studies are required to confirm these preliminary findings and refine treatment protocols.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to restrictions imposed by the institution's privacy policy and ethical guidelines but are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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