Clinical and radiological outcomes of proactive Gamma Knife surgery for asymptomatic meningiomas compared with the natural course without intervention

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OBJECTIVE This study aimed to verify the effect of proactive Gamma Knife surgery (GKS) in the treatment of asymptomatic meningioma compared with the natural course without any therapeutic intervention.

METHODS From January 2006 to May 2017, 354 patients newly diagnosed with asymptomatic meningioma were reviewed and categorized into GKS (n = 153) and observation (n = 201) groups. Clinical and radiological progression rates were examined, and changes in volume were analyzed.

RESULTS Clinical progression (i.e., clinician-judged progression), combining symptomatic progression (n = 43) and clinician-judged increase in size using images routinely acquired (n = 34), occurred in 4 patients (2.6%) and 73 patients (36.3%) in the GKS and observation groups, respectively (p < 0.001). The clinical progression-free survival (PFS) rates in the GKS and observation groups were 98.7% and 64.6%, respectively, at 5 years (p < 0.001), and 92.9% and 42.7%, respectively, at 10 years (p < 0.001). The radiological tumor control rate was 94.1% in the GKS group, and radiological progression was noted in 141 patients (70.1%) in the observation group. The radiological PFS rates in the GKS and observation groups were 94.4% and 38.5%, respectively, at 5 years (p < 0.001), and 88.5% and 7.9%, respectively, at 10 years (p < 0.001). Young age, absence of calcification, peritumoral edema, and high T2 signal intensity were correlated with clinical progression in the observation group. Volumetric analysis showed that untreated tumors gradually increased in size. However, GKS-treated tumors shrank gradually, although transient volume expansion was observed in the first 6 months. Adverse events developed in 26 of the 195 GKS-treated patients (13.3%), including 1 (0.5%) major event requiring microsurgery due to severe edema after GKS. Peritumoral edema was related to the development of adverse events (p = 0.004).

CONCLUSIONS Asymptomatic meningioma is a benign disease; however, nearly two-thirds of patients experience tumor growth and one-third of untreated patients eventually require neurosurgical interventions during watchful waiting. GKS can control tumors clinically and radiologically with high probability. Although the risk of transient adverse events exists, proactive GKS may be a reasonable treatment option when there are no comorbidities limiting life expectancy.

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KEYWORDS asymptomatic meningioma; proactive Gamma Knife surgery; natural history; stereotactic radiosurgery

MENINGIOMA is the most common incidental neoplasm encountered in the neurosurgical field.²¹ Traditionally, microsurgery is the preferred treatment for meningioma, and gross-total resection of the tumor results in a high probability of tumor control.¹⁰ Due to advances in neuroimaging technology and increased frequency of neurological checkups, detection of asymp-

tomatic meningioma is becoming more common. Initial treatment options are observation with regular imaging follow-up, surgery, and stereotactic radiosurgery (SRS), considering the situation of each individual patient. In most cases, asymptomatic meningioma has an indolent natural course, and it is unusual that surgery is recommended immediately after diagnosis.^{2,7,11,20} Because SRS

ABBREVIATIONS CI = confidence interval; CPA = cerebellopontine angle; GKS = Gamma Knife surgery; HR = hazard ratio; PFS = progression-free survival; RoV = ratio of volume to initial volume; SI = signal intensity; SRS = stereotactic radiosurgery.

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is less invasive than surgery and can be performed easily on asymptomatic patients, proactive SRS might have a beneficial aspect. However, the choice of SRS as an initial treatment for the asymptomatic meningioma remains controversial.

The efficacy of SRS as primary and adjuvant therapy for surgically unfavorable small- to medium-sized meningiomas is well established, and shows an equivalent tumor control rate compared with Simpson Grade I resection.^{1,4,8,9,16,19} Some authors reported that primary SRS for asymptomatic meningioma is highly effective in tumor control and has an acceptable rate of complications.^{7,17} However, most of the reported results come from a single-arm study including only SRS-treated groups compared with historical controls with microsurgery and/or radiotherapy. Therefore, to further determine the efficacy of SRS as a proactive treatment and to assist in clinical decision making at the time of diagnosis, we designed a single-institute retrospective cohort study comprising patients with newly diagnosed asymptomatic meningioma, who underwent treatment with one of two different initial therapeutic options.

Methods

Patient Selection and Data Collection

This retrospective study analyzed 687 patients with asymptomatic meningioma for whom medical records were available for the period between January 2006 and May 2017. Meningioma was diagnosed based on the presence of definite radiological features of meningioma, such as extraaxial lesion, dural tail, and good contrast enhancement. "Asymptomatic" was defined as the absence of symptoms or signs, with the exception of mild nonspecific symptoms such as headache and dizziness that were not related to the specific location of tumors. A total of 687 patients were given concise explanations regarding the known natural course of meningioma and were offered three options for treatment: microsurgery, Gamma Knife surgery (GKS), and watchful waiting. The treatment was decided independently by the patient and family members after the discussion with neurosurgeons. Of the 687 patients, those who underwent surgical treatment at the time of initial diagnosis, those who previously received conventional radiation treatment, and those who had neurofibromatosis Type II genetic mutation were excluded. Patients whose initial and last MRI results were unavailable for volumetric analysis were also excluded. In addition, patients who were unavailable to undergo imaging series for more than a year were excluded because of the slow-growing nature of meningioma. Finally, 354 patients were eligible to be analyzed in this study (Fig. 1). The mean age and proportion of women among the 333 excluded patients were 57.4 ± 12.0 years and 75.4%, respectively. These values were not statistically different from those of the included patients.

The patients were divided into two groups: observation and GKS. The observation group consisted of 201 patients with initially untreated asymptomatic meningioma who underwent regular follow-up with MRI. The GKS group consisted of 153 patients initially treated using Gamma

FIG. 1. Patient selection flow chart. NF = neurofibromatosis; RT = radiotherapy.

Knife (Leksell Gamma Knife model C, Perfection or ICON; Elekta AB). The clinical and radiological data of patients were retrospectively collected from medical records and MRI review. Follow-up MRI and clinical evaluations were typically obtained at 12 and 24 months, and then every other year thereafter. Additionally, early MRI, i.e., 3 to 6 months after radiosurgery, was performed for GKS-treated patients. In patients treated with GKS, marginal dose (Gy) and the percentage to the prescribed isodose line were investigated. A neurosurgeon determined the tumor locations, and the state of calcification, T2 signal intensity (SI), and peritumoral edema were assessed based on the initial MRI. Calcification was confirmed by referring to CT scans, fast-field echo MRI sequences, and susceptibility-weighted imaging MRI sequences in any time course. High T2 SI was classified by comparison with normal gray matter. Positive peritumoral edema was regarded as showing high T2 or T2 FLAIR SI in the adjacent brain parenchyma. The study protocol was reviewed and approved by the IRB of Samsung Medical Center. The informed consent requirement was waived.

Survival and Subgroup Analysis

The estimated survival rates of the two groups were evaluated under intention-to-treat analysis. Clinical progression (clinician-judged progression) was defined as the time when resection or GKS was required due to the following: 1) symptomatic progression, defined as newly developing neurological deficits or uncontrolled preexisting symptoms even without change in size; or 2) clinician-judged increase in size, defined as a trend toward tumor growth in subsequent MRI scans agreed upon by both neurosurgeons and radiologists.

Radiological progression was defined by only considering a volumetric change of more than 30% increase when compared with the initial volume. The limit of volumetric progression as 30% was set because a 10% increase in di-

ameter was assumed to cause an increase of approximately 33% in the volume of a spherical tumor. Radiological progression in the GKS-treated group was confirmed only after the radiation effects disappeared. The progression or last follow-up date for radiological evaluation was determined based on the date of MRI scan.

To predict and compare the rate of loss to follow-up in the two groups, a survival analysis was performed in which loss to follow-up was the event of interest, with patients censored at treatment or death. Loss to follow-up was defined as patients not undergoing a scheduled MRI scan. To evaluate possible factors related to clinical and radiological progression in the natural course of the untreated patients, univariate and multivariate analyses were performed. In addition, for patients who received GKS as the initial treatment or salvage treatment after progression, adverse events and related factors were investigated.

Volumetric Analysis

Tumor volume was measured using the GKS planning program, Leksell Gamma Plan (Elekta AB). For patients who received GKS at either initial diagnosis or progression, the treatment planning volume was considered the initial volume or the volume at progression, respectively. Treatment planning was performed by expert neurosurgeons with specialized experience in radiosurgery. In other MRI series, source images were imported to the above-mentioned program and used as planning references. The majority of the imported images were T1-enhanced axial images. T2 or T2 FLAIR images were used when T1-enhanced series were not performed. A neurosurgeon and an experienced assistant traced the tumor margin in each slice using a drawing tool. To reduce measurement errors, contours of the same mass in serial images were obtained in the same manner (e.g., the same extent of dural enhancement or bone invasion). A variable named RoV (ratio of volume to initial volume), which is the volume of interest divided by the initial volume, was created because the study focused on comparison of relative change of volume instead of absolute volume. To verify the accuracy of our measurements, both examiners assessed 100 serial images of 38 patients, and paired values of RoV were statistically evaluated. The intraclass correlation coefficient was 0.928 ($p < 0.001$).

To obtain the line graph, the time interval from the initial diagnostic image to the serial image was measured, and the corresponding RoV for each measured series was calculated. We divided the follow-up time into 6, 12, 24, 36, 48, 60, 90, and 120 months, and the remainder, and obtained the mean values of RoV for each time interval. The time intervals and corresponding mean RoV with 95% confidence interval (CI) were used to create a graph using commercial software (Microsoft Excel 2010, Microsoft Corp.).

Statistical Analysis

Data were presented as the number of patients with percentages for categorical variables, mean $\pm$ standard deviation for parametric continuous variables, and median with range for nonparametric variables. The independent

samples t-test and the Mann-Whitney U-test were used for normally distributed variables and nonparametric variables, respectively. The chi-square test was applied in comparing nominally distributed categorical variables. The Kaplan-Meier method was applied for survival analysis, and the Cox proportional hazards model and logistic regression analysis were used for univariate and multivariate analyses. All statistical analyses were performed using PASW software (version 18.0.0, SPSS Inc.) and a 2-sided p value of 0.05 was used as the threshold for significance in all tests.

Results

Patient Population

Of the 354 patients, 77 (21.8%) were male and 277 (78.2%) were female. The mean age was 57.6 ± 9.3 years, and the median clinical follow-up time was 57 months (range 12–24 months). A total of 183 patients (51.7%) were diagnosed with meningioma via brain imaging during health checkup, and the other 171 patients presented with mild or nonspecific symptoms. No statistical differences were noted between the GKS and observation groups in terms of age, sex, cause of diagnosis, or follow-up time (Tables 1 and 2).

The median initial tumor volume of overall patients was 1.7 ml, and the GKS group showed a significantly larger median volume than the observation group ($p < 0.001$). In terms of radiological features, no difference was noted between the groups in the proportion of calcified masses. However, high T2 SI ($p = 0.009$) and peritumoral edema ($p = 0.001$) were more frequently detected in the GKS group than in the observation group (Table 1).

Tumor locations are listed in Table 1, and the convexity was the most popular lesion site, followed by the falx and parasagittal regions. Petroclival lesion included clival meningioma ($n = 1$), and cerebellar lesion included meningioma at the foramen magnum ($n = 1$) and the jugular foramen ($n = 1$). The olfactory groove, planum sellae, and tuberculum sellae meningiomas were regarded as frontal base meningiomas. Sphenoid ridge and anterior clinoid masses were considered middle fossa meningiomas. Convexity lesions were significantly more common in the observation group than in the GKS group. Cerebellopontine angle (CPA), petroclival, and intraventricular meningiomas were more likely to be treated with GKS ($p < 0.001$).

Clinical Progression (clinician-judged progression)

Overall 77 patients experienced clinical progression during follow-up, and 43 (55.8%) showed symptomatic progression. Thirty-four patients (44.2%) showed clinician-judged increase in size without symptoms. Among the 43 patients who became symptomatic, 7 developed neurological deficits such as limb weakness or numbness, facial pain, and decreased visual acuity due to the mass. The other 36 patients showed persistence of nonspecific symptoms such as headache, dizziness, disequilibrium, and scalp paresthesia (Table 2).

In the GKS group, 4 patients (2.6%) developed clinical progression during a median follow-up period of 53 months. In contrast, 73 patients (36.3%) in the observation

TABLE 1. Characteristics of 354 patients with asymptomatic meningioma

Characteristic	Overall (n = 354)	GKS (n = 153)	Observation (n = 201)	p Value
Mean age in yrs (SD)	57.6 (9.3)	56.6 (7.4)	58.3 (10.4)	0.062*
Female, n (%)	277 (78.2)	119 (77.8)	158 (78.6)	0.851†
Health checkup, n (%)	183 (51.7)	78 (51.0)	105 (52.2)	0.814†
Median initial volume in ml (range)	1.7 (0.1–47.4)	2.5 (0.22–38.1)	1.0 (0.1–47.4)	<0.001‡
High T2 SI, n (%)	157 (44.4)	80 (52.3)	77 (38.3)	0.009†
Calcification, n (%)	123 (34.7)	48 (31.4)	75 (37.3)	0.245†
Peritumoral edema, n (%)	34 (9.6)	24 (15.7)	10 (5.0)	0.001†
Tumor location, n				<0.001†
Convexity	103	15	88	
Falx/parasagittal	103	50	53	
CPA	44	30	14	
Petroclival	11	9	2	
Cerebellar	11	2	9	
Frontal base	24	13	11	
Tentorial	14	10	4	
Middle fossa	29	12	17	
Cavernous sinus	4	4	0	
Intraventricular	11	8	3	
GKS				
No. performed	195	154§	41	
Median dose in Gy (range)	14 (10–22)	14 (10–22)	14 (12–17)	0.344‡
Median % isodose line (range)	50 (15–60)	50 (15–60)	50 (46–50)	0.221‡
Lost to follow-up, n (%)	70 (19.8)	32 (20.9)	38 (18.9)	0.638†

* Independent t-test.

† Chi-square test.

‡ Mann-Whitney U-test.

§ Including one salvage GKS.

group experienced progression during a median follow-up of 62 months ($p < 0.001$). The clinical tumor control rate was 97.4%. Among the 4 patients with clinical progression after GKS, 2 progressed early, i.e., before 1 year (5 and 8 months). The remaining 2 experienced progression approximately 10 years after GKS (105 and 129 months). One of the 2 patients who showed progression later was treated with microsurgery at 105 months, and a transitional meningioma was confirmed. The other patient received a second GKS at 129 months of follow-up, and the tumor was stable at the last follow-up.

One of the patients who progressed early (at 5 months after GKS) was a 53-year-old woman who showed a convexity meningioma 6 ml in size. The mass contained calcification and showed iso-T2 SI with edema. After GKS with 13 Gy to the 50% isodose line, she developed a headache that was controlled with steroids and painkillers. However, MRI after 5 months revealed severely increased edema, and the tumor volume had increased to 7.7 ml. Microsurgical resection was performed safely, and the mass was histologically determined to be a meningiothelial meningioma. This case was considered the major adverse event of GKS.

The other patient who experienced early disease progression was a 54-year-old woman who had a medium-sized petroclival meningioma (8.1 ml). She received 12

Gy of radiation to the 50% isodose line. Neither immediate side effects nor peritumoral edema was noted until 6 months after GKS. However, she gradually experienced facial dysesthesia and pain on the same side of the mass that did not respond to pain killers, carbamazepine, and gabapentin. After 8 months, the tumor volume increased to 10.3 ml, and a clinician recommended microsurgery. However, the patient refused surgery and chose to take medication only. She was followed up for more than 4 years, and neuralgia was well managed at the last clinic visit.

In the observation group, among the 73 patients who experienced clinical progression, 41 and 13 received GKS and microsurgery, respectively. The remaining 19 patients were recommended to undergo neurosurgical intervention, but they refused further treatment. Among the 13 patients who received microsurgery, histological data were available in all cases, and all patients were diagnosed with WHO Grade I meningioma (5 cases of fibrous, 4 meningiothelial, and 4 transitional meningiomas).

The actuarial clinical progression-free survival (PFS) rates at 3, 5, and 10 years in the GKS group were 98.7%, 98.7%, and 92.9%, respectively, because no events were noted between 8 months and 105 months. Meanwhile, in the observation group, the 3-, 5-, and 10-year actuarial

TABLE 2. Summary of clinical and radiological progression

Variable	Overall (n = 354)	GKS (n = 153)	Observation (n = 201)	p Value
Median clinical follow-up in mos (range)	57 (12–224)	53 (12–177)	62 (12–224)	0.350*
Clinical progression, n (%)	77 (21.8)	4 (2.6)	73 (36.3)	<0.001†
Median estimated clinical PFS (mos)		NA	104	<0.001‡
Actuarial clinical PFS rate (%)				
At 3 yrs		98.7	79.6	<0.001§
At 5 yrs		98.7	64.6	<0.001§
At 10 yrs		92.9	42.7	<0.001§
Symptomatic progression, n (%)	43/77 (55.8)	3/4 (75)	40/73 (54.8)	0.428†
Symptoms at progression, n				
Unspecified symptoms	36	1	35	
Neurologic symptoms	7	2	5	
No symptoms	34	1	33	
Median radiologic follow-up in mos (range)	47 (11–212)	46 (12–177)	47 (11–212)	0.670*
Radiological progression, n (%)	150 (42.4)	9 (5.9)	141 (70.1)	<0.001†
Median estimated PFS (mos)		NA	45	<0.001‡
Actuarial radiological PFS rate (%)				
At 3 yrs		94.4	60.2	<0.001§
At 5 yrs		94.4	38.5	<0.001§
At 10 yrs		88.5	7.9	<0.001§
Mean RoV at last examination (SD)		0.87 (0.27)	1.78 (1.15)	<0.001¶

NA = not applicable.

* Mann-Whitney U-test.

† Chi-square test.

‡ Log-rank test.

§ Z-test.

¶ Independent t-test

clinical PFS rates were 79.6%, 64.6%, and 42.7%, respectively. The p value obtained using the Z-test with PFS rate and its standard error showed a significant difference at each time point ($p < 0.001$). The estimated median clinical PFS in the observation group was 104 months (95% CI 80.3–127.7 months). Kaplan-Meier survival curves are shown in Fig. 2A ($p < 0.001$, log-rank test). The hazard ratio (HR) for no treatment was 13.840 (95% CI 5.056–37.885; $p < 0.001$).

Radiological Progression

Overall, 150 patients (42.4%) showed radiological progression. A total of 9 (5.9%) and 141 (70.1%) patients experienced radiological progression in the GKS and observation groups, respectively (Table 2, $p < 0.001$). The radiological tumor control rate of the GKS group was 94.1%. All 4 GKS-treated patients who experienced clinical progression also showed radiological progression.

The actuarial radiological PFS rates at 3, 5, and 10 years in the GKS group were 94.4%, 94.4%, and 88.5%, respectively. In the observation group, the actuarial radiological PFS rates at 3, 5, and 10 years were 60.2%, 38.5%, and 7.9%, respectively. The estimated median radiological PFS was 45 months (95% CI 59.6–74.3 months) in the observation group. Significant survival benefits of GKS were noted at the 3-, 5-, and 10-year follow-ups ($p < 0.001$). The HR of the observation group compared with the GKS-treated group was 15.803 (95% CI 8.046–31.037; $p <$

0.001). Survival curves are shown in Fig. 2B ($p < 0.001$, log-rank test).

Factors Related to the Progression

Because only 4 cases of clinical progression were noted in the GKS group, univariate and multivariate analyses were performed only in the observation group. In univariate analysis, young age, absence of calcification, and high T2 SI were significantly correlated with poor prognosis, and the presence of peritumoral edema showed a trend toward significance. Sex and initial tumor volume were not correlated with clinical progression. In multivariate analysis, all of the above-mentioned related factors were significantly correlated with clinical progression. However, none of these factors were related to radiological progression (Table 3).

Analysis of Loss to Follow-Up

A total of 70 patients (19.8%) were lost to follow-up, and there was no difference in the rate of loss to follow-up between the two groups (Table 1 and Fig. 3). The actuarial rates of follow-up at 3, 5, and 10 years were 93.2%, 79.2%, and 67.2% in the GKS group, respectively. In the observation group, the actuarial rates of follow-up at 3, 5, and 10 years were 88.2%, 83.6%, and 61.6%, respectively. In multivariate analysis, older age was the only predictive factor for loss to follow-up (HR 1.043, 95% CI 1.017–1.070; p

FIG. 2. Kaplan-Meier curves for clinical (A) and radiological (B) PFS in the GKS and observation (OBS) groups (both $p < 0.001$, log-rank test). Solid lines and dashed lines indicate GKS and OBS groups, respectively. GKS-treated patients show the better prognosis with time. Figure is available in color online only.

= 0.001), while treatment group, tumor location, calcification, peritumoral edema, high T2 SI, and initial tumor volume were not related.

Adverse Events of GKS

A total of 195 GKSs were performed; of those, 153 were initially performed and 42 were salvage treatments. Adverse events occurred in 26 cases (13.3%), and 18 of them were headache and/or dizziness. Transient neurological deficits possibly related to the mass, such as limb paresthesia, confusion, dysarthria, and trigeminal neuralgia, devel-

oped in 6 patients. Two patients had short-term hair loss. Severe edema requiring surgical intervention, which was considered a serious adverse event after GKS, occurred in 1 (0.5%) patient. All other adverse events (25 of 26, 96.2%) were transient, and no permanent sequelae remained after treatment with steroids for 1 week to a maximum of 3 months. In univariate and multivariate analyses, the occurrence of adverse events was correlated with the presence of peritumoral edema (HR 4.885, 95% CI 1.660–14.376; $p = 0.004$), but it was not correlated with calcification ($p = 0.459$); tumor located in the convexity, falx, and parasagittal area ($p = 0.398$); or high T2 SI ($p = 0.757$).

TABLE 3. Summary of factors related to clinical and radiological progression in observation group

Factor	Univariate p Value	Clinical Progression		Radiological Progression	
		HR (95% CI)	p Value	HR (95% CI)	p Value
Young age	0.047	1.025 (1.002–1.047)	0.033*	1.005 (0.989–1.022)	0.512
Absence of calcification	<0.001	2.262 (1.142–4.480)	0.019*	0.983 (0.653–1.480)	0.935
Peritumoral edema	0.058	2.829 (1.262–6.346)	0.012*	1.450 (0.696–3.021)	0.321
High T2 SI	<0.001	2.044 (1.210–3.454)	0.008*	1.315 (0.890–1.944)	0.169
Sex	0.640	NA		NA	
Initial tumor volume	0.142	NA		NA	

Young age, absence of calcification, peritumoral edema, and high T2 SI were related to clinical progression, whereas sex and initial volume of tumor were not.

* Statistically significant.

Number at risk

GKS	153	81	23	3	0	0
OBS	201	93	27	7	4	0

FIG. 3. Kaplan-Meier curves for loss to follow-up in the GKS (solid line) and observation (OBS, dashed line) groups. There was no difference between the two groups. Figure is available in color online only.

Volumetric Analysis

Volumetric analysis was available in 1171 series. At least two series of initial and last follow-up were available, and a maximum of nine serial images were analyzed. We derived 817 coordinates consisting of follow-up time and corresponding RoV. The number of items and mean values of each interval with 95% CIs are listed in Table 4. In the

first 6 months, no significant difference was noted between the mean RoV of the two groups, and an even larger volume expansion was observed in the GKS group. However, in the following time periods there was a stepwise increase in the tumor volume in cases of untreated meningioma, whereas GKS-treated meningiomas showed gradual shrinkage with significant statistical differences (Fig. 4).

Discussion

The method for treating asymptomatic meningiomas is more important nowadays because of the increased incidental detection of them. It is already well known that GKS is an effective treatment for meningioma. Stafford et al. reported a 93% 5-year local tumor control rate in 190 patients with benign meningioma, and half of them showed decreased tumor size. GKS-related complications, including cranial neuropathies, were present in 13% of the patients.¹⁹ Recently, meaningful observational studies were conducted. Kondziolka et al. reported 10- and 20-year PFS rates of 87.7% and 87.2%, respectively, with only 6% of the 34 asymptomatic patients in their study becoming symptomatic among the 290 GKS-treated patients.⁸ Pollock et al. reported 3 cases of tumor progression among 251 patients and a 72.1% decrease in tumor size after GKS during a mean follow-up period of 62.9 months.¹⁵ In a meta-analysis of SRS for benign meningiomas, the local control rate was reported to range from 86% to 100% at 5 years and 83% to 95% at 10 years with a complication rate of 2%–23%.¹ The overall tumor control rate and the actuarial PFS rates of the GKS group in the present study are in accordance with those of other reports.

The rate of adverse events in this study is also similar to those reported in other studies.^{1,2} Notably, the development of only 1 case (0.5%) of serious complication in the GKS group in our study is a much better outcome than the known major complication rate of microsurgery.^{2,12,18} Chang et al. reported that radiological adverse events developed in 25% of GKS-treated lesions, and adverse events were mostly seen after treating lesions in the convexity,

TABLE 4. List of mean values of each follow-up time interval for drawing volumetric curve

Time Interval (mos)	GKS Group		Observation Group		p Value
	No. of Items	Mean (95% CI)	No. of Items	Mean (95% CI)	
0–6	32	1.21 (1.08–1.34)	20	1.18 (0.96–1.39)	0.741
6–12	53	1.08 (1.00–1.17)	54	1.35 (1.22–1.47)	<0.001
12–24	93	0.94 (0.88–0.99)	83	1.40 (1.29–1.51)	<0.001
24–36	46	0.97 (0.87–1.06)	71	1.60 (1.43–1.84)	<0.001
36–48	56	0.85 (0.77–0.93)	50	1.85 (1.54–2.15)	<0.001
48–60	31	0.88 (0.73–1.04)	42	1.71 (1.52–2.07)	<0.001
60–90	32	0.77 (0.66–0.87)	73	2.00 (1.79–2.27)	<0.001
90–120	16	0.87 (0.56–1.18)	30	2.46 (1.72–3.34)	<0.001
>120	15	0.87 (0.67–1.08)	20	2.52 (2.15–3.23)	<0.001
Total	374		443		

At 6 months after GKS, the mean volume of treated tumor was greater than that of untreated tumor and there was no difference statistically ($p = 0.741$). However, GKS-treated meningiomas shrunk after initial increase in volume, and the size was maintained for over 10 years, whereas untreated masses expanded gradually with time. All comparisons were performed using independent t-tests.

FIG. 4. Volumetric changes with time in the GKS and observation (OBS) groups. The mean values of RoV at each follow-up time interval are presented with 95% CIs in the timeline chart. *Square pointers and dashed line* indicate the OBS group, whereas *circle pointers and solid line* indicate the GKS group. Figure is available in color online only.

parasagittal, and falx areas.³ In our factor analysis, GKS-treated lesions originating from the convexity, falx, and parasagittal areas were not related to increased occurrence of adverse events. This finding may be explained by the smaller size of tumors in our study, even though these lesions were located in the area vulnerable to radiation-induced complications. Additionally, patients with convexity meningiomas tended to choose observation without treatment because they were informed that the surgery for convexity lesions would not be accompanied with a high surgical risk in cases of tumor growth.

The presence of edema prior to GKS was found to be a risk factor for the occurrence of adverse events. Carefully managing patients with a high probability of adverse events and judging patients who require additional neurosurgical intervention in advance is important. Checking the MRI scan during the early period is recommended to prevent major complications. In our institution, we routinely performed MRI scans at 3 to 6 months after GKS.

The natural course of asymptomatic meningioma was evaluated in the 201 untreated patients. Most meningiomas (70.1%) expanded with time, and nearly one-third of the patients (36.3%) eventually required neurosurgical intervention. In particular, tumors showing unfavorable features, such as young age, absence of calcification, high T2 SI, and presence of edema, had a high probability of eventually requiring treatment. Some authors reported better prognosis of untreated meningioma. Reported radiological progression rates varied from 22.2% to 37.3%.^{6,13,22,23} Some authors suggested that conservative management, with avoidance of surgical morbidity, might be the best option. However, paradoxically, these results can be interpreted as nearly one-third of asymptomatic meningiomas expanded

and were ultimately treated. In the largest recent article on incidental meningiomas, growth of more than 2 mm was observed in 44% of 273 incidental meningiomas, and volumetric growth more than 8.2% was noted in 74% of cases. In that study, the growth-related factors were young age, absence of calcification, T2 SI, and edema, which coincide with our results.¹⁴ Some authors conducted serial volumetric assessments in terms of natural history of incidental meningioma, and they found that 62.9% of 70 patients showed tumor growth with complex growth patterns.⁵ The aim of that study was different from ours, but the ratio of radiologically progressed mass was similar.

Although the definition of progression has varied among studies, our results showed a trend of higher probability of progression than other studies. It might have resulted from the role of our hospital as a national referral center. Patients without progression may not have been referred to our institution. However, with time, a number of untreated patients are often referred to our institution when disease progression occurs during observation. This circumstance would have affected the outcome of the present study.

Methods to predict the course of asymptomatic meningioma and whether asymptomatic patients really need treatment are important issues. Some authors suggested that GKS had to be applied to lesions more likely to develop symptoms.¹⁷ A valuable meta-analysis of Sughrue et al. revealed that 42% of asymptomatic patients with tumors 2–2.5 cm in diameter with an annual growth rate of higher than 10% became symptomatic. Additionally, only 2% of the patients with initial tumor diameters < 2 cm progressed to worse or new symptoms. The authors concluded that leaving small-sized asymptomatic meningiomas untreated, with regularly checking MRI scans to

evaluate growth, is a reasonable treatment option instead of subjecting patients to radiation.²⁰ To date, this type of treatment (observation with regular imaging follow-up) is considered reasonable in treating asymptomatic meningioma, and it is controversial whether SRS is an overtreatment or not.

However, there are several reasons to perform proactive GKS for asymptomatic patients. Repeated MRI follow-up throughout a patient's lifetime is essential for an untreated mass because the tumor prognosis cannot be accurately predicted. However, in clinical practice, there are patients with low compliance who cannot always be followed up at a given time. These patients may not receive clinical attention until symptomatic progression, and only resection without other alternatives may be possible in that situation. In contrast, it is possible to consider omission of follow-up MRI scans after GKS with much lower risk, because 97.4% of masses treated with proactive GKS require no further intervention. Therefore, proactive GKS has an advantage in terms of fewer clinic visits and fewer MRI scans over the patient's lifetime. In addition, clinicians and patients may be relieved of a psychological burden after noninvasive treatment, whereas untreated patients may always maintain a fear of tumor growth.

Our study was a retrospective study and was subject to the limitations inherent to this study design. As this was a single-institution study, the results are subject to the selection bias of our clinicians, although patients were allowed to make their own decisions regarding treatment. Correspondingly, proactive GKS was performed more actively in younger patients. The mean age of the observation group showed a trend toward older age than that of the GKS group ($p = 0.062$). The rate of loss to follow-up was related to older age, although the HR was not high. According to our philosophy, we would like to emphasize that proactive GKS should be applied with consideration of life expectancy. For patients who are expected to have a long-term life expectancy—in other words, patients who have no comorbidities limiting life expectancy—GKS can be considered preemptively before the development of symptoms.

Furthermore, as shown in patients' characteristics, initial tumor volume, presence of peritumoral edema, and high T2 SI were significantly different between the two groups. These differences also reflected the preferences of neurosurgeons. However, because peritumoral edema and high T2 SI were unfavorable factors for PFS, and were more prevalent in the GKS group, the effect of GKS might hold further promise despite selection bias. Propensity matching to compare the two groups would yield more reliable results. However, propensity matching in this cohort using the nearest matching algorithm resulted in other limitations. Statistical power decreased because nearly 30% of patients were unmatched and excluded from analyses. In addition, the median volume of GKS-treated masses was significantly greater than that of untreated masses even after propensity matching. Instead, in the present study, we focused on the relative results of two strategies selected in the beginning. We believe that discussion of the results depending on the initial clinical choice of treatment has great implications for clinicians.

Despite the limitations of the current study, it is evident that GKS significantly changes the natural course and reduces the probability of tumor growth in asymptomatic meningiomas. The results of our study suggest that proactive GKS is a reasonable option preferable to observation without intervention if the selection of patients is conducted carefully, considering the risk factors for complications.

Conclusions

Asymptomatic meningioma is a benign disease, but nearly one-third of untreated asymptomatic meningiomas eventually require treatment. As GKS showed promising effects clinically and radiologically with an acceptable risk of adverse events, proactive GKS may be a reasonable treatment option for asymptomatic meningioma when there is no significant comorbidity limiting life expectancy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Lee, Kim. Acquisition of data: Kim, Kang. Analysis and interpretation of data: Lee, Kim, Kang. Drafting the article: Lee, Kim. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lee. Statistical analysis: Kim. Study supervision: Lee.

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