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Gamma Knife radiosurgery for intracranial benign meningiomas: follow-up outcome in 130 patients

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OBJECTIVE The authors retrospectively analyzed the follow-up data in 130 patients with intracranial benign meningiomas after Gamma Knife radiosurgery (GKRS), evaluated the tumor progression-free survival (PFS) rate and neurological function preservation rate, and determined the predictors by univariate and multivariate survival analysis.

METHODS This cohort of 130 patients with intracranial benign meningiomas underwent GKRS between May 2012 and May 2015 at the Second Hospital of Tianjin Medical University. The median age was 54.5 years (range 25–81 years), and women outnumbered men at a ratio of 4.65:1. All clinical and radiological data were obtained for analysis. No patient had undergone prior traditional radiotherapy or chemotherapy. The median tumor volume was 3.68 cm^3 (range 0.23–45.78 cm^3). A median margin dose of 12.0 Gy (range 10.0–16.0 Gy) was delivered to the tumor with a median isodose line of 50% (range 50%–60%).

RESULTS During a median follow-up of 36.5 months (range 12–80 months), tumor volume regressed in 37 patients (28.5%), was unchanged in 86 patients (66.2%), and increased in 7 patients (5.4%). The actuarial tumor progression-free survival (PFS) rate was 98%, 94%, and 87% at 1, 3, and 5 years, respectively, after GKRS. Tumor recurred in 7 patients at a median follow-up of 32 months (range 12–56 months). Tumor volume ≥ 10 cm^3 ($p = 0.012$, hazard ratio [HR] 8.25, 95% CI 1.60–42.65) and pre-GKRS Karnofsky Performance Scale score < 90 ($p = 0.006$, HR 9.31, 95% CI 1.88–46.22) were independent unfavorable predictors of PFS rate after GKRS. Of the 130 patients, 101 (77.7%) presented with one or more neurological symptoms or signs before GKRS. Neurological symptoms or signs improved in 40 (30.8%) patients, remained stable in 83 (63.8%), and deteriorated in 7 (5.4%) after GKRS. Two (1.5%) patients developed new cranial nerve (CN) deficit. Tumor volume ≥ 10 cm^3 ($p = 0.042$, HR = 4.73, 95% CI 1.06–21.17) and pre-GKRS CN deficit ($p = 0.045$, HR = 4.35, 95% CI 0.84–22.48) were independent unfavorable predictors for improvement in neurological symptoms or signs. Six (4.6%) patients developed new or worsening peritumoral edema with a median follow-up of 4.5 months (range 2–7 months).

CONCLUSIONS GKRS provided good local tumor control and high neurological function preservation in patients with intracranial benign meningiomas. Patients with tumor volume < 10 cm^3, pre-GKRS Karnofsky Performance Scale score ≥ 90, and no pre-GKRS CN deficit (I–VIII) can benefit from stereotactic radiosurgery. It can be considered as the primary or adjuvant management of intracranial benign meningiomas.

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KEYWORDS stereotactic radiosurgery; Gamma Knife radiosurgery; benign meningioma

Meningioma, the most common primary intracranial benign tumor in adults,[36] arises from the dura mater. Currently, a craniotomy is still the preferred treatment for meningioma. The optimal outcome is to achieve a maximal resection of the tumor and for the neurological function to be left intact. However, it is usually difficult for neurosurgeons to achieve a gross-total resection due to large tumor size, deep tumor location, and proximity to critical structures. The overall gross-total resection rate of meningiomas in previous studies in the literature varied from 40% to 96%,[1,14,17,23,28,39] and craniotomy is sometimes accompa-

ABBREVIATIONS ARE = adverse radiation effect; CN = cranial nerve; CPA = cerebellopontine angle; GKRS = Gamma Knife radiosurgery; HR = hazard ratio; KPS = Karnofsky Performance Scale; PFS = progression-free survival; SRS = stereotactic radiosurgery.

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TABLE 1. Characteristics of 130 patients with intracranial benign meningiomas treated with GKRS

Characteristic	Value (%)
Female:male	107:23 (82:18)
Age in yrs	
≥60 vs <60	37:93 (28.5:71.5)
Median	54.5
Range	25–81
Previous resection	53 (40.8)
Previous radiotherapy	0
Previous GKRS	0
Symptomatic patients*	101 (77.7)
Headache	35 (26.9)
Dizziness	30 (23.1)
CN deficit	50 (38.5)
CN I	2 (1.5)
CN II	16 (12.3)
CN III, IV, & VI	18 (13.9)
CN V	26 (20)
CN VII	1 (0.8)
CN VIII	5 (3.8)
Limb weakness	9 (6.9)
Sensory disturbance	7 (5.4)
Seizure	3 (2.3)
Hypomnesia	3 (2.3)
Ataxia or balance disorder	2 (1.5)
Tumor distribution	
Single vs multiple	107:23 (82.3:17.7)
Total no. of tumors	156
No previous resection	83 (53.2)
Residual or progressive	73 (46.8)
Tumor location	
Convexity area	26 (16.7)
Parafalcine & parasagittal	28 (17.9)
Sellar & parasellar	27 (17.3)
Petroclival	23 (14.7)
CPA	21 (13.5)
Tentorial	16 (10.2)
Foramen magnum	2 (1.3)
Sphenoidal	10 (6.4)
Olfactory	3 (1.9)
Tumor vol in cm^3	
≥10 vs <10	48:108 (30.8:69.2)
Median	3.68
Range	0.23–45.78
No resection	
Median	2.6
Range	0.23–21.1
Residual or progressive	
Median	8.90
Range	0.33–45.78
Median follow-up duration in mos	36.5, range 12–80
KPS score	
<90 vs ≥90	15:115 (11.5:88.5)
Mean ± SD	90.5 ± 6.7
Range	50–100

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TABLE 1. Characteristics of 130 patients with intracranial benign meningiomas treated with GKRS

* 101 (77.7%) symptomatic patients presented with one or more neurological symptoms or signs before GKRS.

nied by postoperative complications, neurological dysfunction, tumor recurrence, and death.[2,4,6,18,23,24,42] Stereotactic radiosurgery (SRS) provides a minimal invasion, is a more efficient treatment, and has fewer complications for patients with intracranial meningiomas, and is now attracting increasing attention from neurosurgeons. SRS provides radiobiological tumor growth control by delivering highly conformal radiation in a single procedure. The sharp falloff of radiation beyond the planning target volume reduces long-term radiation-related complications. Gamma Knife radiosurgery (GKRS) is now increasingly used for the treatment of intracranial meningiomas due to its precise positioning of intracranial lesions. This is a single-center outcome study of the midterm efficacy of GKRS in the treatment of benign intracranial meningiomas.

Methods

Patient Population

This cohort was composed of 130 patients with intracranial WHO grade I meningiomas who underwent GKRS at the Second Hospital of Tianjin Medical University between May 2012 and May 2015. The characteristics and clinical features of the patients are presented in Table 1. Patients were excluded for follow-up time < 6 months or pathological grading ≥ WHO grade II—exceptional cases of death due to intracranial meningioma or patients with tumor recurrence were included in spite of a follow-up period < 6 months. All patients were diagnosed as harboring a benign meningioma based on the natural course of the disease, radiological features, and histopathology. The typical natural course of benign meningioma includes a long medical history, slow tumor progression, and no history of cancer metastasis. Radiological features include a dural tail sign, clear boundaries, and uniform contrast enhancement on MRI sequences obtained with contrast agents. Radiological features that distinguish benign meningioma from atypical or malignant meningioma include relatively small tumor volume, mild peritumoral edema, and absence of tumor necrosis, whereas atypical or malignant meningiomas often exhibit invasive growth characteristics that destroy the surrounding brain parenchyma and skull. Sometimes a conventional MRI histogram analysis based on a 3D tumor measurement can help the differential diagnosis.[11,20,44]

Gamma Knife Procedure

In this study, all patients were first evaluated by neurosurgeons and radiologists for radiosurgery. The indications for patients undergoing radiosurgery were as follows: 1) tumor diameter < 3 cm in patients with no severe neurological symptoms or signs; 2) residual or recurrent tumors after craniotomy; and 3) patients unwilling or unable to tolerant a resection.

A Gamma Knife Model C unit (Elekta Instruments, Inc.) was used before July 2014 and a Gamma Knife Perfexion unit (Elekta Instruments, Inc.) was used thereafter in the treatment of patients with meningiomas. The GKRS procedure began with the placement of a Leksell Model G stereotactic frame (Elekta AB), which was attached to the patient's head after local anesthesia and sedation, and then 2-mm-slice, no gap, high-resolution stereotactic contrast-enhanced MRI was performed to determine the location of intracranial lesions and their relationship with surrounding critical structures. Rarely, a 64-slice CT scan was performed when the patient had a metal implant or was allergic to gadopentetate. Thin-slice axial and coronal plane images were obtained and transferred to GammaPlan Station software. Radiosurgical dose planning was performed by a neurosurgeon in conjunction with a radiation oncologist and a medical physicist. All patients in this cohort underwent a single session of SRS, tumor volume was computed by contouring the tumor and then using GammaPlan Station software, and the optimal margin dose and isodose line were determined by tumor volume and adjacent critical structures according to the dose-volume effect. The median prescribed dose delivered to the tumor margin was 12.0 Gy (range 10.0–16.0 Gy, < 9.0 Gy for cranial nerve [CN] II) with a median isodose line of 50% (range 50%–60%) and a median of 7 isocenters (range 4–28) (Table 2). Each patient was administered 40 mg corticosteroid intravenously before SRS.

TABLE 2. GKRS treatment parameters

Characteristic	Median ± SD (range)
Margin dose in Gy	12.0 ± 1.0 (10.0–16.0)
Maximum dose in Gy	24.0 ± 2.0 (18.2–32.0)
Isodose line in %	50 ± 2.5 (50–60)
No. of isocenters	7 ± 2.8 (4–28)

Clinical and Radiological Follow-Up

All patients who underwent GKRS were regularly followed up on an outpatient basis every 6 months in the 1st year, and yearly thereafter if the tumor was well controlled or there was no evidence of neurological symptoms or signs of deterioration. The termination of follow-up was at tumor recurrence or the patient's death due to intracranial meningiomas. Clinical follow-up was performed by a neurosurgeon who assessed the patient's symptoms or signs, neurological function, and Karnofsky Performance Scale (KPS) score to determine whether further intervention was needed. At the time of radiological follow-up, the patients underwent a thin-slice, high-resolution enhanced MRI or CT scan, and the neuroimaging outcome was evaluated by a neurosurgeon or neuroradiologist and compared with the neuroimaging obtained at GKRS to determine whether the tumor recurred or progressed, or whether there were adverse radiation effects (AREs). AREs were defined as new or worsening peritumoral edema that shows high intensity on T2-weighted or FLAIR MRI sequences after GKRS. Parameters of tumor control were defined as 1) tumor progression (tumor volume increased ≥ 10% compared to the volume at GKRS); 2) tumor regression (tumor volume shrinkage ≥ 10%); or 3) tumor unchanged (tumor volume change < 10%).[5,30,34] There was no distant metastasis. Tumor volume was computed by measuring the maximum diameter at the horizontal, coronal, and sagittal planes of the MR images. Tumor volume (cm^3) = anteroposterior diameter × horizontal diameter × vertical diameter (cm) × $\pi/6$.

Statistical Analysis

Event occurrence at follow-up was defined as tumor recurrence or progression. Description analysis of continuous variables was done using the mean or median in case of normal or nonnormal distributions, respectively, and categorical variables were described by frequencies and percentage. The follow-up time for patients with event occurrence was calculated from the first GKRS to event (tumor recurrence, tumor progression, or patient's death), and for the others it was calculated from the first GKRS to the last follow-up. All time-to-event data were calculated from the time of first GKRS to tumor recurrence, and were described with a Kaplan-Meier survival curve. Univariate Kaplan-Meier survival analysis was performed first to identify potential predictive factors for tumor recurrence or progression; variables with a $p \leq 0.2$ were considered meaningful and entered into the multivariate Cox regression analysis to assess hazard ratios (HRs).[13] The multivariate proportional hazards model was built by a prior consideration of the predictors for which data were gathered. Continuous data were compared using the Student t-test; categorical data were compared using the chi-square test. All calculations were performed using commercially available statistical software (IBM SPSS Statistics 20, IBM Corp.), and $p < 0.05$ was considered statistically significant.

Results

Patient and Tumor Attributes

At the time of data collection, a total of 130 patients with intracranial WHO grade I meningiomas were included in the study, among whom 2 patients died of chronic medical diseases unrelated to intracranial tumors, one at 46 and the other at 67 months after GKRS. Of the 130 patients with a median age of 54.5 years (range 25–81 years), women outnumbered men at a ratio of 4.65:1 (107:23). A total of 77 (59.2%) patients underwent GKRS as primary management, and 53 (40.8%) patients received it as adjuvant or salvage management (45 with residual tumors and 8 with progressive tumors) after resection; the tumors in the latter group were pathologically proven to be WHO grade I meningioma. The median interval between primary resection and radiosurgery was 5 months (range

TABLE 3. Specific alterations of tumor volume on radiological imaging after GKRS

Characteristic	Shrinkage	Stable	Progression	Overall (%)
No. of patients	37	86	7	130
No. of tumors*	37	112	7	156
Convexity area	1	23	2	26 (16.7)
Parafalcine & parasagittal	5	22	1	28 (17.9)
Sellar & parasellar	11	16	0	27 (17.3)
Petroclival	8	13	2	23 (14.7)
CPA	6	15	0	21 (13.5)
Tentorial	5	10	1	16 (10.2)
Foramen magnum	0	2	0	2 (1.3)
Sphenoidal	0	10	0	10 (6.4)
Olfactory	1	1	1	3 (1.9)

* 156 tumors were treated with GKRS, for 23 patients with multiple tumors.

1–52 months). There was at least one neurological symptom, sign, or CN deficit in 101 (77.7%) patients before GKRS, including headache (26.9%), dizziness (23.1%), limb weakness (6.9%), sensory disturbance (5.4%), seizure (2.3%), hypomnesia (2.3%), CN deficits (I–VIII) (38.5%), and other symptoms or signs (ataxia, balance disorder) (1.5%). The mean KPS score was 90.5 ± 6.7 (range 50–100) before GKRS. No patient had received prior adjuvant radiotherapy or chemotherapy.

A total of 156 tumors with a median tumor volume of 3.68 cm^3 (range 0.23–45.78 cm^3), consisting of 48 (30.8%) large tumors (volume ≥ 10 cm^3) and 108 (69.2%) small and moderate tumors (volume < 10 cm^3) were under treatment by GKRS.[30] Categorized by tumor site, the percentages were as follows: convexity meningiomas (16.7%), parafalcine and parasagittal meningiomas (17.9%), sellar and parasellar meningiomas (17.3%), petroclival meningiomas (14.7%), cerebellopontine angle (CPA) meningiomas (13.5%), tentorial meningiomas (10.2%), foramen magnum meningiomas (1.3%), sphenoidal meningiomas (6.4%), and olfactory meningiomas (1.9%).[21,22,41] There were 73 (46.8%) residual or progressive tumors with a median volume of 8.9 cm^3 (range 0.33–45.78 cm^3), and 83 (53.2%) initial tumors with a median volume of 2.6 cm^3 (range 0.23–21.1 cm^3).

Radiological Outcomes

Radiological follow-up was usually performed in parallel with clinical follow-up. During a median follow-up duration of 36.5 (range 12–80) months, tumor volume was observed to have shrunk in 37 (28.5%) patients, remained unchanged in 86 (66.2%) patients, and increased in 7 (5.4%) patients (Table 3). Of the patients with tumor recurrence, the median recurrence time from GKRS was 32 (12–56) months. Tumor recurred within the planning target volume in 5 patients and outside the planning target volume in 2; there was no case of distant recurrence. For further interventions, 4 of 7 patients with tumor recurrence underwent a second GKRS and the rest preferred microsurgical resections, which were then accompanied by a second GKRS for the residual tumors. All tumors were well controlled at the last follow-up.

In this study the tumor progression-free survival (PFS) rate was used to evaluate the local tumor control. Tumor PFS was defined as the time from the GKRS to tumor recurrence or progression. The cumulative PFS rates of the whole cohort at 1, 3, and 5 years by Kaplan-Meier survival analysis were 98%, 94%, and 87%, respectively. Univariate Kaplan-Meier analysis of predictive variables revealed that tumor volume ≥ 10 cm^3 ($p = 0.012$, HR 8.25, 95% CI 1.60–42.65) (Fig. 1) and patient KPS score < 90 ($p = 0.006$, HR 9.31, 95% CI 1.88–46.22) (Fig. 2) were independent unfavorable predictors for tumor progression, and multivariate Cox regression analysis also pointed to the same result (Table 4).

Clinical Outcomes

The number of patients with neurological symptoms, signs, or CN deficit before GKRS in this cohort was 101 (77.7%); the specific symptoms, signs, or CN deficit are shown in Table 1. Among this subgroup 38 (37.6%) patients had prior tumor resection, in which 12 patients developed new or worsening of preexisting neurological symptoms and signs after resection; and 63 (62.4%) patients had no craniotomy history. During a median follow-up of 36.5 months neurological symptoms, signs, or CN deficit were improved in 40 (30.8%) patients, remained stable in 83 (63.8%), and deteriorated in 7 (5.4%) (Table 5); the actuarial neurological function preservation rate was 94.62%. Among the patients with deteriorative symptoms or signs, 3 patients developed new CN deficits after GKRS—one had facial numbness and difficulty in opening the mouth 24 months after GKRS, another developed worsening visual acuity at the 9th month, and the third patient experienced diplopia at the 16th month. All 3 patients were regularly observed every 3–6 months, and 2 of them presented with no progression in CN deficit, whereas the third patient developed progressive symptoms. This patient's tumor was found to recur at the 55th month of radiological follow-up, and a further craniotomy was performed. At the last follow-up, the mean KPS score of the cohort was 92.5 ± 7.8, compared to the mean KPS score of 90.5 ± 6.7 at GKRS by t-test with statistical significance ($p = 0.01$).

To determine the predictive factors for neurological symptoms or signs of deterioration, univariate Kaplan-Meier survival analysis and multivariate Cox regression analysis were used and found that preexisting CN deficit ($p = 0.045$, HR 4.35, 95% CI 0.84–22.48) and tumor volume ≥ 10 cm^3 ($p = 0.042$, HR 4.73, 95% CI 1.06–21.17) were independent unfavorable predictors for neurological symptoms or signs of deterioration in this cohort. Patient age, craniotomy history, pre-GKRS KPS score, and margin dose were of no statistical significance to the deterioration of neurological symptoms or signs (Table 6).

Of the 40 patients with neurological symptoms or signs who improved following GKRS, in 13 patients tumor volume shrinkage was also observed on neuroimaging; the rest had a stable tumor volume. Among the 7 patients with neurological symptoms or signs of deterioration, tumor volume increased in 4 patients and remained stable in 3.

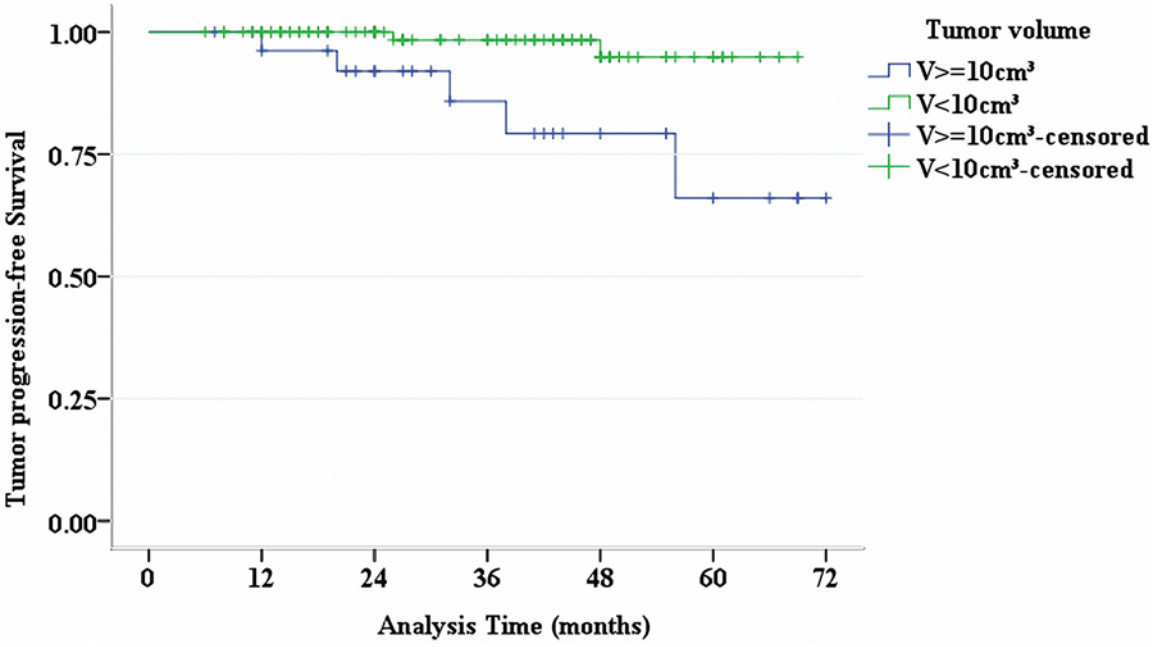

FIG. 1. Graph of tumor PFS in patients stratified by tumor volume of 10 cm^3. V = volume.

Therefore, the deterioration of neurological symptoms or signs was not always consistent with the increase of tumor volume.

Adverse Radiation Effects

AREs usually include radiation-induced brain parenchymal and peritumoral edema or necrosis. There was no obvious preexisting peritumoral edema before GKRS in this cohort. During the radiological follow-up, 6 (4.6%) patients were observed with new peritumoral edema at a median follow-up of 4.5 months (range 2–7 months), 5 of whom were asymptomatic and needed no intervention, whereas another person presented with limb weakness and was given oral corticosteroids for 1 month. All peritumoral edema lasted for a median time of 6 months (range 4–15 months) and then disappeared. We attempted to identify the predictive factors for AREs by univariate

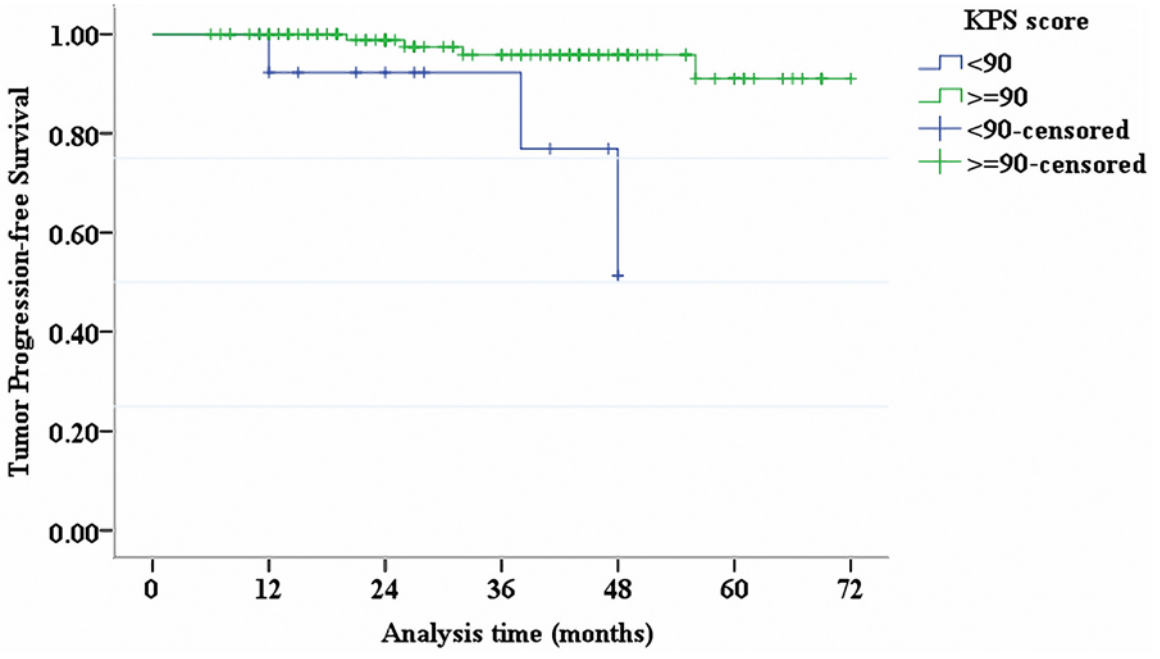

FIG. 2. Graph of tumor PFS in patients stratified by KPS score of 90.

TABLE 4. Predictors of tumor progression after GKRS by univariate and multivariate analysis

Analysis & Pre-GKRS Variables	p Value	HR (95% CI)
Univariate		
Age (≥60 vs <60 yrs)	0.363	2.00 (0.45–9.01)
Prior craniotomy (yes vs no)	0.214	2.84 (0.55–14.72)
CN deficit pre-GKRS (yes vs no)	0.768	1.25 (0.28–5.62)
Tumor volume (≥10 vs <10 cm^3)	0.012*	8.25 (1.60–42.65)
KPS score (<90 vs ≥90)	0.006*	9.31 (1.88–46.22)
Margin dose (<12.0 vs ≥12.0 Gy)	0.434	1.93 (0.37–9.97)
Multivariate		
Prior craniotomy (yes vs no)	0.380	2.45 (0.33–18.46)
Tumor volume (≥10 vs <10 cm^3)	0.027*	5.97 (1.62–31.44)
KPS score (<90 vs ≥90)	0.008*	7.74 (2.51–26.34)

* Statistically significant ($p < 0.05$).

TABLE 6. Predictors of neurological symptoms or signs of deterioration after GKRS by univariate and multivariate analysis

Analysis & Pre-GKRS Variables	p Value	HR (95% CI)
Univariate		
Age (≥60 vs <60 yrs)	0.979	0.98 (0.19–5.04)
Prior craniotomy (yes vs no)	0.153	3.30 (0.64–17.02)
CN deficit pre-GKRS (yes vs no)	0.045*	4.35 (0.84–22.48)
Tumor volume (≥10 vs <10 cm^3)	0.042*	4.73 (1.06–21.17)
KPS score (<90 vs ≥90)	0.656	1.62 (0.19–13.44)
Margin dose (<12.0 vs ≥12.0 Gy)	0.499	1.76 (0.34–9.09)
Multivariate		
Prior craniotomy (yes vs no)	0.348	2.30 (0.40–13.13)
CN deficit pre-GKRS (yes vs no)	0.027*	3.2 (0.57–18.35)
Tumor volume (≥10 vs <10 cm^3)	0.016*	3.35 (0.60–18.57)

* Statistically significant ($p < 0.05$).

and multivariate analysis, but no statistically significant outcome was found.

Other Radiation Complications

Five (3.8%) patients experienced acute radiation toxicity within a few hours after the GKRS procedure. Two patients developed nausea and vomiting, another patient had a rapid deterioration of visual acuity, the fourth experienced transient facial paralysis, and the last had a deterioration of preexisting facial numbness. Acute radiation toxicity was usually treated with corticosteroids and mannitol or glycerol fructose intravenously, and the symptoms were often relieved within 1 week. One patient developed intermittent seizures due to peritumoral edema 6 months after GKRS, and the symptoms disappeared after using corticosteroids and antiepileptic drugs intravenously for 2 days (now she takes oral antiepileptic drugs regularly to prevent further seizures). There was no evidence of distant tumor recurrence or metastasis, or of radiation-induced tumor malignancy.

TABLE 5. Specific alterations in clinical neurological symptoms or signs after GKRS

Characteristic	Improvement	Stable	New or Worsening	Overall (%)
No. of patients	40	83	7	130
Asymptomatic	0	29	0	29 (22.3)
Symptomatic*	40	54	7	101 (77.7)
Headache	18	16	1	35 (26.9)
Dizziness	21	9	0	30 (23.1)
Limb weakness	3	5	1	9 (6.9)
Sensory disturbance	2	5	0	7 (5.4)
Seizure	1	2	0	3 (2.3)
Hypomnesia	0	3	0	3 (2.3)
CN deficit	11	34	5	50 (38.5)
I	0	2	0	2 (1.5)
II	1	13	2	16 (12.3)
III, IV, & VI	4	13	1	18 (13.9)
V	7	17	2	26 (20)
VII	0	1	0	1 (0.8)
VIII	1	4	0	5 (3.8)
Ataxia/balance disorder	1	1	0	2 (1.5)

The mean KPS score was 92.5 ± 7.8 (range 50–100) at the last follow-up.
* 101 (77.7%) symptomatic patients presented with one or more neurological symptoms or signs before GKRS.

Discussion

Meningioma is one of the most common intracranial primary tumors. So far, microsurgery is still the preferred treatment for meningiomas. However, gross-total resection of meningiomas—especially those located at the skull base—remains a great challenge for neurosurgeons and, in addition, microsurgery is usually accompanied with morbidity and mortality.[19,27,43] SRS provides an alternative treatment for both initial and residual or progressive tumors. Because of the good local tumor control rate and neurological function preservation of SRS, more neurosurgeons accept the comprehensive treatment strategy of microsurgery combined with radiosurgery.[9,15,25]

Some recent studies that were focused on the treatment of intracranial meningiomas with radiosurgery reported that the local tumor control rates ranged from 88% to 100%, in which 19%–74% of tumors shrank during a mean follow-up of 36–78 months.[3,7,12,21,22,30–34,37,39–41] In a single-center study, Hasegawa et al.[12] reported an actuarial PFS rate of 92%, 86%, and 72% at 3, 5, and 10 years, respectively, in 67 patients. In a meta-analysis of SRS for skull base meningiomas, Starke et al.[41] reviewed the outcome in 469 patients with large skull base meningiomas (> 8 cm) from several centers, and reported that the actuarial tumor PFS rates at 3, 5, and 10 years were 90.3%, 88.6%, and 77.2%, respectively. Haselsberger et al.[13] treated 20 patients with intracranial giant meningioma (median 33.3 cm^3, range 13.6–79.8 cm^3) by staged GKRS with a median margin dose of 12.0 Gy (range 10.0–14.0 Gy) and achieved

a 90% local tumor control rate during a median 9.5-year follow-up. In the present study, the tumor PFS rates at 1, 3, and 5 years were 98%, 94%, and 87%, respectively, which is similar to previous studies in midterm follow-up.

For the predictors of tumor recurrence or progression, some studies revealed that increasing tumor volume was an independent predictor, which was also proved in our study.[10,16,29] In this study, many patients with intracranial meningiomas had low subjective acceptance of craniotomy; even though there were significant mass effect or neurological symptoms or signs, they preferred GKRS instead of craniotomy, which resulted in a high rate of large tumor (≥ 10 cm^3) in proportion at the time of GKRS, and reduced the treatment effect of GKRS in the cohort. In addition, a GKRS dose-plan defect may also influence local tumor control. Usually there is no clear boundary between meningioma and its adjacent dura mater, or when the tumor is in close proximity to critical structures such as CNs, major cortical draining veins, hypothalamus, and brainstem, these may lead to incomplete coverage of tumor volume within the isodose line or limitation of tumor margin dose, and then the tumor may recur or progress outside the planning target volume. In view of the great success achieved by Haselsberger et al. in treating intracranial giant meningiomas, a new strategy was provided for the treatment of intracranial large meningiomas (≥ 10 cm^3) with staged GKRS.

An unexpected result of this study is that a pre-GKRS KPS score < 90 became another unfavorable independent predictor for tumor recurrence or progression. We hypothesized that for patients with a KPS score < 90, the initial or residual tumors were usually in close proximity to or compressing the adjacent critical structures, especially motor or language cortex, CN II, superior sagittal sinus, cavernous sinus, and brainstem, and this could lead to damage to the neurological function, which limited the coverage of tumor within the planning target volume and the margin dose delivered to tumors. This hypothesis is consistent with the outcome of clinical observations.

A favorable outcome is defined as no tumor progression and no deterioration of neurological symptoms or signs. In contrast, any tumor progression, new-onset or worsening neurological symptoms or signs, and severe AREs or radiation complication was considered an unfavorable outcome. In this study, 7 patients experienced new or worsening neurological symptoms or signs, and 2 of them were evaluated for tumor progression on neuroimaging, whereas 5 patients had tumor recurrence or progression on neuroimaging without neurological symptoms or signs of deterioration, and there were no severe AREs or radiation complications. Thus, an unfavorable outcome was observed in 12 patients (9.2%), compared to the favorable outcome in 118 patients (90.8%); this result is similar to the previous studies.[8,13,35] The univariate and multivariate analysis discussed above had revealed that tumor volume ≥ 10 cm^3, pre-GKRS CN deficits (I–VIII), and KPS score < 90 were independent predictors for an unfavorable outcome.

Five patients developed acute radiation toxicity within a few hours after the GKRS procedure; symptoms or signs included headache, vomiting, damage of visual acuity, transient peripheral facial paralysis, and worsening of preexisting facial numbness. Six patients had new peritumoral edema during a median follow-up of 4.5 months (range 2–7 months) after the GKRS procedure; the peritumoral edema disappeared within 1 year in 5 asymptomatic patients with regular observation, and after administration of corticosteroids 1 symptomatic patient was cured at the 6-month follow-up. There were no radiation-related deaths in this series. The incidence of AREs was 8.5% (Table 7). Sheehan et al.[38] reported on 212 patients who underwent GKRS for parasagittal and parafalcine meningiomas, of whom 11 patients (5.2%) had new or worsening peritumoral edema during a median follow-up period of 19.6 months (range 6–158 months). In a multicenter study, Milano et al.[26] analyzed the follow-up data of SRS on the treatment of non–skull base meningiomas and indicated that the incidence of peritumoral edema ranged from 5% to 43% within 3–9 months following SRS. The results of these reports support the consensus that GKRS is a safe and effective treatment choice for intracranial benign meningiomas due to its low morbidity and mortality rates.

TABLE 7. Radiation-related complications following GKRS and intervention

Complication	Value (%)	Treatment
Acute radiation reaction		
Headache	1 (0.8)	Corticosteroid
Vomiting	1 (0.8)	Corticosteroid
Damage of visual acuity	1 (0.8)	Corticosteroid
Transient peripheral facial paralysis	1 (0.8)	Corticosteroid
Deterioration of pre-existing facial numbness	1 (0.8)	Corticosteroid
Peritumoral edema		
Worsening	0	
New		
Asymptomatic	5 (3.8)	Observation
Symptomatic	1 (0.8)	Corticosteroid
Overall	11 (8.5)	

Study Limitations

The present work is a retrospective cohort study with inherent selection bias—patients who underwent GKRS as primary treatment in this cohort lacked histopathological evidence, and imaging-based diagnosis of meningiomas does not guarantee a completely accurate diagnosis and distinguish between benign and atypical meningiomas, which may lead to the inclusion of other intracranial benign tumors such as schwannomas. This study had a long time span, and during this time the center experienced staff turnover, instrument and software upgrades, and improvement in SRS techniques, which may have an influence on the treatment strategy. In addition, there was not a uniform objective standard for the assessment of neurological symptoms or signs, and an accurate algorithm for tumor volume on neuroimaging was lacking, which may lead to outcome data bias. The follow-up time was not long enough to estimate the long-term outcome of GKRS on

meningiomas. Finally, this is a single-center study, so the results are not scalable.

Conclusions

GKRS provides a safe and effective solution for intracranial WHO grade I meningioma with its good local tumor control, high neurological function preservation, and low morbidity and mortality rates. Patients with tumor volume < 10 cm^3, pre-GKRS KPS score ≥ 90, and no pre-GKRS CN deficits (I–VIII) can benefit from GKRS. Therefore, it can be considered a primary treatment for asymptomatic patients with tumor volume < 10 cm^3, an alternative treatment for patients who are subjectively unwilling or unable to undergo craniotomy, or as an adjuvant treatment of residual and progressive tumor after craniotomy. We expect more data from multiple centers and longer follow-up time to support this conclusion.

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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: D Liu, Ge, Zhang, Wang. Acquisition of data: Ge, Zhang, Lin. Analysis and interpretation of data: Ge, Wang. Drafting the article: Ge. Critically revising the article: D Liu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: D Liu. Statistical analysis: Li, Lin, Zong. Administrative/technical/material support: D Liu, Ge, Zhang, Li, Lin, Wang, Zong. Study supervision: D Liu, Zhang.

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