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Original Article

The Role of Gamma Knife Radiosurgery in the Management of Grade 2 Meningioma

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Abstract

Background and objectives: The role of radiosurgery in the treatment of grade 2 meningioma remains unclear. This study aimed to evaluate the long-term outcomes of gamma knife radiosurgery (GKRS) in patients with grade 2 meningiomas and to identify factors influencing tumor control and survival.

Methods: In this retrospective study, seventy patients underwent GKRS for grade 2 meningioma between 2007 and 2016. Tumor recurrence was categorized as local, marginal, or distant. Survival curves were estimated using the Kaplan-Meier method, while the log-rank test and Cox proportional hazards model were employed to analyze potential risk factors.

Results: The median follow-up period was 48 months (range: 8 to 132 months). The one-year, three-year, and five-year local control rates were 92%, 73%, and 65%, respectively. The one-, three-, and three-year progression-free survival rates were 87%, 51%, and 44%, respectively. Multiple lesions and multiple prior recurrences were identified as negative predictors of marginal control and progression-free survival. Similarly, multiple lesions and marginal doses ≤13 Gy were associated with poor local control. Serious complications related to gamma knife use occurred in 4% of patients.

Conclusions: Our results support that GKRS is a reasonable treatment option in the management of grade 2 meningiomas. However, outfield progression remains a significant challenge, particularly in patients with multiple prior relapses and/or multiple lesions. More aggressive treatment strategies should be explored for these high-risk patients.

Introduction

Meningiomas are the most common primary intracranial neoplasms in adults, accounting for more than 30% of all intracranial neoplasms.[1,2] According to the World Health Organization (WHO) grading system, meningiomas are classified into three grades based on specific histological criteria: WHO grade 1 (benign), WHO grade 2 (atypical), and WHO grade 3 (malignant).[3,4] Grade 2 meningiomas are defined by increased mitotic activity and/or distinctive histological features. Clear cell and chordoid subtypes are also classified as grade 2 meningiomas. In the 2007 and 2016 WHO classifications, brain invasion was included as an independent criterion for grade 2 (atypical) meningiomas. This revision in classification has increased the proportion of grade 2 meningiomas from 7% to 15–20%.[5–7]

Surgical resection, aiming for maximal safe removal of the tumor, remains the primary treatment for grade 2 meningiomas. However, unlike benign meningiomas, grade 2 meningiomas exhibit a significant tendency for recurrence, even after radical surgical resection with or without adjuvant radiotherapy (RT). Stereotactic radiosurgery (SRS) has increasingly been used in selected patients for residual or recurrent grade 2 meningiomas as an alternative or adjunct to external beam radiotherapy (EBRT), offering comparable local control rates.[8–11] Despite these advancements, the specific role of radiosurgery in the treatment of grade 2 meningiomas remains unclear. This uncertainty stems from the heterogeneity of patient populations, complex treatment histories, small sample sizes in studies, and the evolving WHO diagnostic criteria for grade 2 meningiomas. A recent multicenter retrospective study examined a large cohort of patients treated with gamma knife radiosurgery (GKRS) for WHO grade 2 meningiomas, providing data on survival rates, progression-free survival (PFS), and the incidence of adverse radiation events. However, this study did not describe the patterns of tumor recurrence, specifically whether recurrence occurred within or outside the irradiation field.[12] In this

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Table 1. Patient and treatment characteristics

Variable	Value
Sex, M/F	31/39
Median age, y [range]	51 [16–77]
Prior surgery resections median [range]	1 [1–4]
1	54
2	12
3	2
4	2
Prior radiation therapy	11
External beam radiation therapy (54–56 Gy)	9
Gamma knife (12–15 Gy)	2
Tumor location	
Convexity	11
Falx/parasagittal	17
Skull base	42
Single vs. multiple lesions	
Single	63
Multiple	7
Prior recurrence	
Group1: adjuvant therapy for residual tumor after initial surgery	24
Group2: salvage therapy for tumor at first recurrence	32
Group3: salvage therapy for tumor at multiple recurrences	14
Treatment characteristic	
Median maximum dose, Gy [range]	28 (18–33)
Median peripheral dose, Gy [range]	13 (9–17)
Median isodose, [range]	50 (40–60)
Median tumor volume, CM^3 [range]	3.9 (0.15–29.9)

F, female; M, male.

study, we evaluated the long-term outcomes of a large series of patients with grade 2 meningiomas treated with GKRS. We analyzed factors affecting tumor control, patterns of recurrence, and survival to further elucidate the role of GKRS in managing these aggressive tumors.

Materials and methods

We retrospectively reviewed records for all patients who underwent GKRS for grade 2 meningioma between January 2007 and December 2016 at Beijing Tiantan Hospital. Patients with neurofibromatosis type 2 were excluded from the study. This study was carried out in accordance with the recommendations of the Declaration of Helsinki (as revised in 2013). This study was approved by Beijing Tiantan Hospital institutional review board (Approval No. KY2020-135-01). The individual consent for this retrospective analysis was waived.

Baseline demographic variables were documented for each patient, including age, gender, tumor location, prior radiation therapy, prior surgical resections, presence of single versus multiple lesions, prior recurrence, and treatment characteristics. A total of 75 patients were identified for this study, but five patients without subsequent radiological follow-up were excluded from the analysis.

Patient demographics

The patient characteristics are summarized in Table 1. Seventy patients were included in this cohort study, comprising 39 females (55.7%) and 31 males (44.3%). The median age was 46 years (range: 16–77 years). These 70 patients had 79 separate foci of grade 2 meningioma treated with GKRS; 63 patients had a single tumor, and seven patients had multiple tumors. Prior RT was administered in 11 patients, including EBRT in nine patients and GKRS in two patients. The median number of prior recurrences was one (range: 0–6). Twenty-four patients underwent adjuvant GKRS for residual tumors at a median of four months (range: 2–6 months) after the initial surgery. Forty-six patients underwent salvage GKRS at a median of 37 months (range: 6–120 months) following initial surgery. Of these 46 patients, 32 experienced a single

recurrence at a median of 18 months (range: 6–84 months), while 14 experienced multiple recurrences at a median of 60 months (range: 14–120 months).

Radiosurgical parameters

A Leksell stereotactic frame was affixed to each patient's skull under local anesthesia. High-resolution, contrast-enhanced magnetic resonance imaging (MRI) with a slice thickness of 2 mm was performed for treatment planning. Patients underwent single-fraction SRS using the Leksell Gamma Knife Model C (Elekta AB) from January 2007 to October 2011, after which the system transitioned to the Leksell Gamma Knife Perfexion (Elekta AB). Treatment planning was conducted using the GammaPlan system (Elekta AB). The prescription dose and isodose lines were selected based on proximity to critical structures, prior radiation therapy, and tumor size. The median prescription dose was 13 Gy (range: 9–17 Gy) delivered to a median isodose line of 50.0% (range: 40–60%). The median maximum dose was 28 Gy (range: 18–33.3 Gy). The median tumor volume was 3.9 cm^3 (range: 0.15–29.9 cm^3).

Follow-up

Patients were advised to undergo MRI and clinical evaluations every six months during the first year after GKRS, followed by intervals of six to twelve months thereafter. Tumor recurrence was defined as an increase in tumor size or the appearance of a new tumor on follow-up MRI after GKRS. Recurrence was classified as local recurrence (tumor enlargement after treatment), marginal recurrence (new tumor outside the target area but within or immediately adjacent to the resection cavity), or distant recurrence (new tumor in distant locations). To minimize variability between scanners and images, tumor shrinkage or growth was defined as a 25% decrease or increase in volume, respectively.

Statistical analysis

The Kaplan–Meier method was used to estimate overall survival (OS), PFS, local control (LC), marginal control (MC), and distant control (DC). OS, PFS, LC, MC, and DC times were calculated from the date of the first GKRS at our hospital. Only the first instance of each recurrence pattern was considered. PFS was calculated per patient, while LC was calculated per lesion. Univariate analysis was performed using the log-rank test for the following factors: sex, age (≤51 vs. >51 years), prior recurrence (Group 1: adjuvant therapy for residual tumors after initial surgery; Group 2: salvage therapy for tumors at first recurrence; Group 3: salvage therapy for tumors at multiple recurrences), tumor volume (≤13 vs. >13 cm^3), margin dose (≤13.0 vs. >13 Gy), maximum dose (≤28 vs. >28 Gy), prior RT (yes vs. no), and tumor location (parasagittal/convexity vs. skull base). Factors with a p-value ≤ 0.05 in univariate analysis were entered into multivariate Cox regression analysis. A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Tumor control and survival

In the current series, the median duration of follow-up was 48 months (range: 8–132 months). Of these 79 foci, follow-up MRI showed that 33 foci (42%) remained stable, 22 foci (28%) decreased, and 24 foci (30%) increased. The total tumor control rate was 70%.

At the time of the last follow-up, tumor recurrence was demonstrated in 39 of 70 (56%) patients. Fifteen patients (21%) died during a median period of 34.5 months (range: 8–72 months) after GKRS, of whom 14 died due to tumor progression and 1 due to an unknown cause.

The occurrence of tumor recurrence was documented as follows: local recurrence in ten patients, marginal recurrence in fifteen patients, distant recurrence in one patient, local + marginal recurrence in eight patients, marginal + distant recurrence in one patient, local + distant recurrence in one patient, and local + marginal + distant recurrence in three patients. Survival curves were calculated to illustrate the time to death and recurrence. The OS rates at one, three, and five years after GKRS were 99%, 88%, and 77%, respectively. The one-, three-, and five-year LC rates were 92%, 73%, and 65%, respectively. The one-, three-, and five-year MC rates were 94%, 63%, and 56%, respectively. The one-, three-, and five-year DC rates were 96%, 92%, and 90%, respectively. The one-, three-, and five-year PFS rates were 87%, 51%, and 44%, respectively.

Risk factors for tumor progression

Univariate analysis using the log-rank test was performed to assess potential risk factors for OS, LC, MC, DC, and PFS (Tables 2, 3; Figs. 1, 2). All factors with $p \leq 0.05$ in the univariate analysis were entered into multivariate Cox regression analysis. Univariate analysis revealed that factors associated with worse OS included age > 51 years ($p = 0.005$), multiple prior recurrences ($p < 0.001$), parasagittal/convexity lesions ($p = 0.025$), prior radiation therapy ($p = 0.008$), and multiple lesions ($p < 0.001$). Multivariate analysis showed that multiple prior recurrences ($p = 0.004$) and age > 51 years (hazard ratio [HR] = 4.0, $p = 0.04$) were independent factors influencing survival.

In univariate analysis, multiple lesions ($p = 0.002$) and margin doses ≤ 13 Gy ($p = 0.012$) were predictive of worse local control. There was also a trend toward worse local control with parasagittal/convexity lesions ($p = 0.073$). The mean peripheral doses were similar for sagittal sinus/convexity lesions (13.4 Gy) and skull-base lesions (13.3 Gy). A paired t-test did not reveal any statistically significant differences at the $p < 0.05$ level. In multivariate Cox regression analysis, multiple lesions (HR = 4.1, $p = 0.004$) and margin doses ≤ 13 Gy (HR = 3.2, $p = 0.016$) were independent negative predictors of local control.

In univariate analysis, multiple lesions ($p = 0.003$) and multiple prior recurrences ($p = 0.004$) were predictive of worse marginal control. In multivariate Cox regression analysis, multiple lesions (HR = 3.9, $p = 0.008$) and multiple prior recurrences ($p = 0.01$) were independent negative predictors of marginal control.

In univariate analysis, multiple lesions ($p = 0.004$), multiple prior recurrences ($p < 0.001$), age > 51 years ($p = 0.009$), and prior radiation therapy ($p < 0.001$) were predictive of worse distant control. Due to the limited number of patients with distant recurrence, multivariate analysis was not performed.

In univariate analysis, multiple lesions ($p = 0.008$), multiple prior recurrences ($p = 0.001$), margin doses ≤ 13 Gy ($p = 0.039$), and prior radiation therapy ($p = 0.02$) were predictive of worse PFS. In multivariate Cox regression analysis, multiple lesions (HR = 2.7, $p = 0.04$) and multiple prior recurrences ($p = 0.015$) were independent predictors of PFS.

There was no significant difference in OS ($p = 0.758$), local control ($p = 0.618$), marginal control ($p = 0.389$), distant control ($p = 0.285$), and PFS ($p = 0.326$) between Group 1 (adjuvant therapy

Table 2. Univariate and multivariate factors associated with MC, DC, and LC

Factors	Marginal control		Distant control		Local control	
	Univariate *p*-value	Multivariate HR, 95% CI,*p*-value	Univariate *p*-value	Multivariate HR, 95% CI (*p*-value)	Univariate *p*-value	Multivariate HR, 95% CI (*p*-value)
Age (years)	0.274	–	0.009	–	0.396	–
Gender	0.102	–	0.551	–	0.172	–
Multiple or single	0.003	3.9,1.4–10.8 (0.008)	0.004	–	0.002	4.1,1.6–10.9 (0.004)
Tumor volume	0.889	–	0.283	–	0.889	–
Margin dose	0.251	–	–	–	0.012	3.2,1.2–8.3 (0.016)
Maximum dose	0.194	–	–	–	0.147	–
Prior recurrence	0.004	$p = 0.01$	$p < 0.001$	–	0.131	–
Group(1)		0.2,0.1–0.6 (0.004)		–		
Group(2)		0.3,0.1–0.8 (0.018)		–		
Group(3)		reference		–		
Prior RT	0.124	–	$p < 0.001$	–	0.762	–
Tumor location	0.402	–	0.338	–	0.073	–

CI, confidence interval; DC, distant control; HR, hazard ratio; LC, local control; MC, marginal control; RT, radiotherapy.

for residual tumor after initial surgery) and Group 2 (salvage therapy for tumor at first recurrence) in the subgroup analysis.

Radiation-related complications and additional treatment

Three patients (4.3%) developed severe radiation-related complications after GKRS. Two patients experienced symptomatic radiation necrosis (worsening hemiparesis, n = 1; increased seizures, n = 1), which was treated with corticosteroids. Both patients had undergone multiple resections and EBRT before GKRS. The third patient had a 3.9 cm left temporal tumor treated with a marginal dose of 11 Gy. Subsequently, the patient developed increased seizures associated with edema and underwent gross total resection. This patient had no previous radiation therapy.

Of the 39 patients with tumor progression, 30 accepted further treatment after GKRS (Fig. 3). The other nine patients elected not to pursue additional treatments. During the follow-up period, 18 patients underwent 19 additional surgical resections for tumor progression (eight local recurrences, three marginal recurrences, four both local and marginal recurrences, one distant recurrence, and two with all three recurrence patterns). Twenty-three patients underwent 33 repeat SRS procedures for tumor progression (10 local recurrences, 19 marginal recurrences, two both local and marginal recurrences, and two distant recurrences). Additionally, two patients underwent adjuvant EBRT after reoperation. Of the 18 pa-

Table 3. Univariate and multivariate factors associated with PFS and OS

Factors	Progression free survival		Overall survival	
	Univariate *p*-value	Multivariate HR, 95% CI (*p*-value)	Univariate *p*-value	Multivariate HR, 95% CI (*p*-value)
Age (years)	0.381	–	0.005	4.0,1.1–15.0 (0.04)
Gender	0.159	–	0.348	
Multiple or single	0.008	2.7,1.0–7.0 (0.04)	$p < 0.001$	4.6,1.0–22.1 (0.054)
Tumor volume	0.485	–	0.597	
Margin dose	0.039	2.0,1.0–4.3 (0.066)	0.087	
Maximum dose	0.522	–	0.891	
Prior recurrence	0.001	$p = 0.015$	$p < 0.001$	$p = 0.04$
group(1)		0.2,0.1–0.6 (0.004)		0.11,0.02–0.59 (0.10)
group(2)		0.3,0.1–0.8 (0.017)		0.09,0.02–0.43 (0.002)
group(3)		–		
Prior RT	0.02	0.7,0.2–2.4 (0.617)	0.008	1.0,0.2–4.3 (1.00)
Tumor location	0.08	–	0.025	2.3,0.8–7.1 (0.14)

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

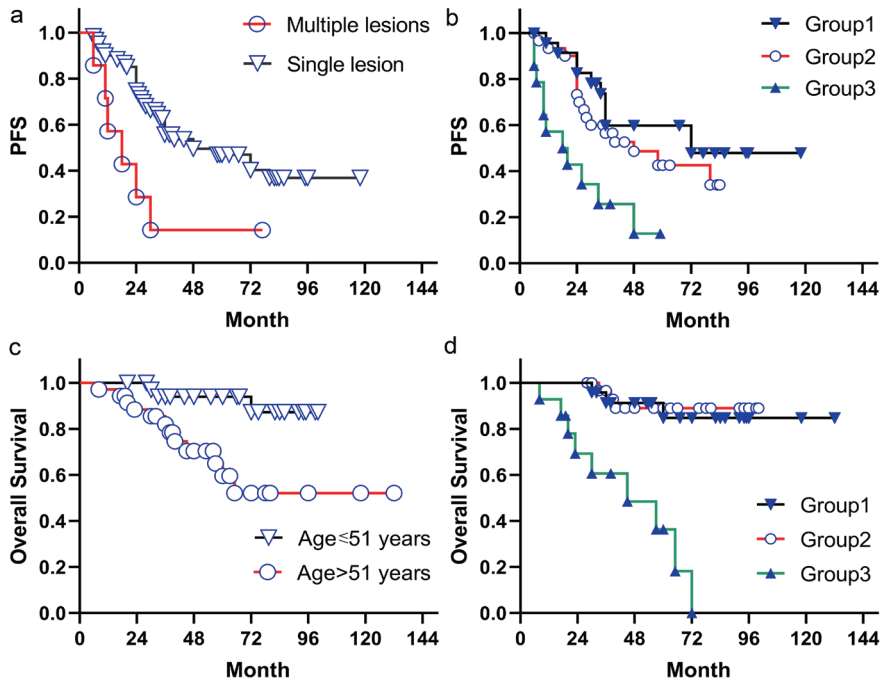

Fig. 1. Kaplan-Meier curves for (a) PFS (p = 0.008) and (d) OS (p < 0.001), comparing single lesions with multiple lesions. Kaplan-Meier curves for (b) PFS (p = 0.01), comparing Group 1: adjuvant therapy for residual tumors after initial surgery/Group 2: salvage therapy for tumors at first recurrence, with Group 3: salvage therapy for tumors at multiple recurrences. Kaplan-Meier curves for (c) OS, comparing age ≤ 51 with age > 51 (p = 0.005). OS, overall survival; PFS, progression-free survival.

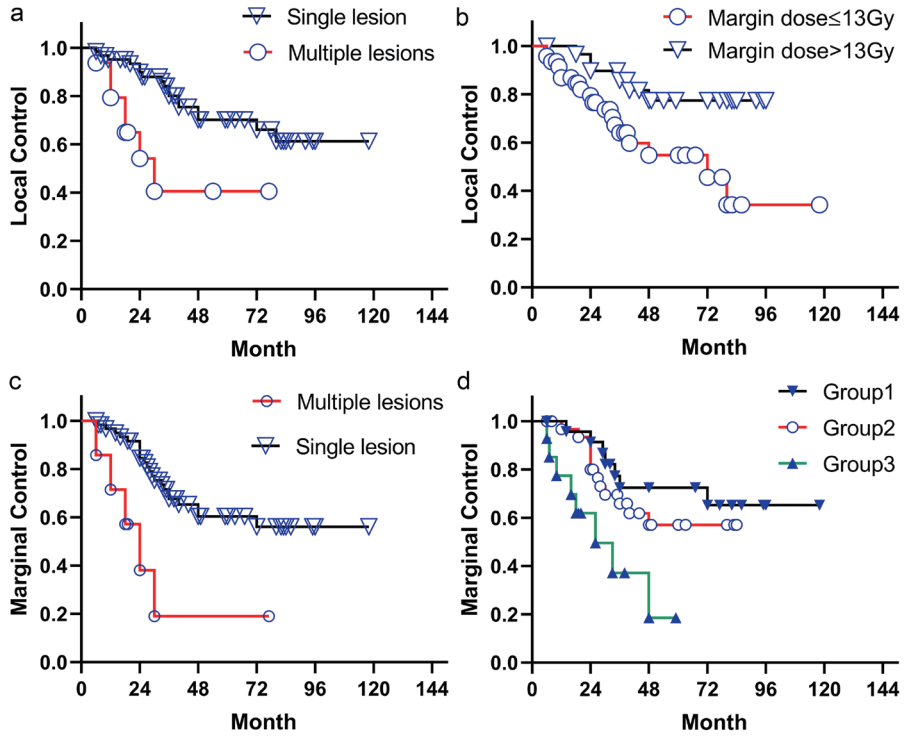

Fig. 2. Kaplan-Meier curves for (a) local control (p = 0.002) and (c) marginal control (p = 0.003), comparing single lesions with multiple lesions. Kaplan-Meier curves for (b) local control, comparing margin doses ≤ 13 Gy with margin doses > 13 Gy (p = 0.002). Kaplan-Meier curves for (d) marginal control (p = 0.005), comparing Group 1: adjuvant therapy for residual tumors after initial surgery/Group 2: salvage therapy for tumors at first recurrence, with Group 3: salvage therapy for tumors at multiple recurrences.

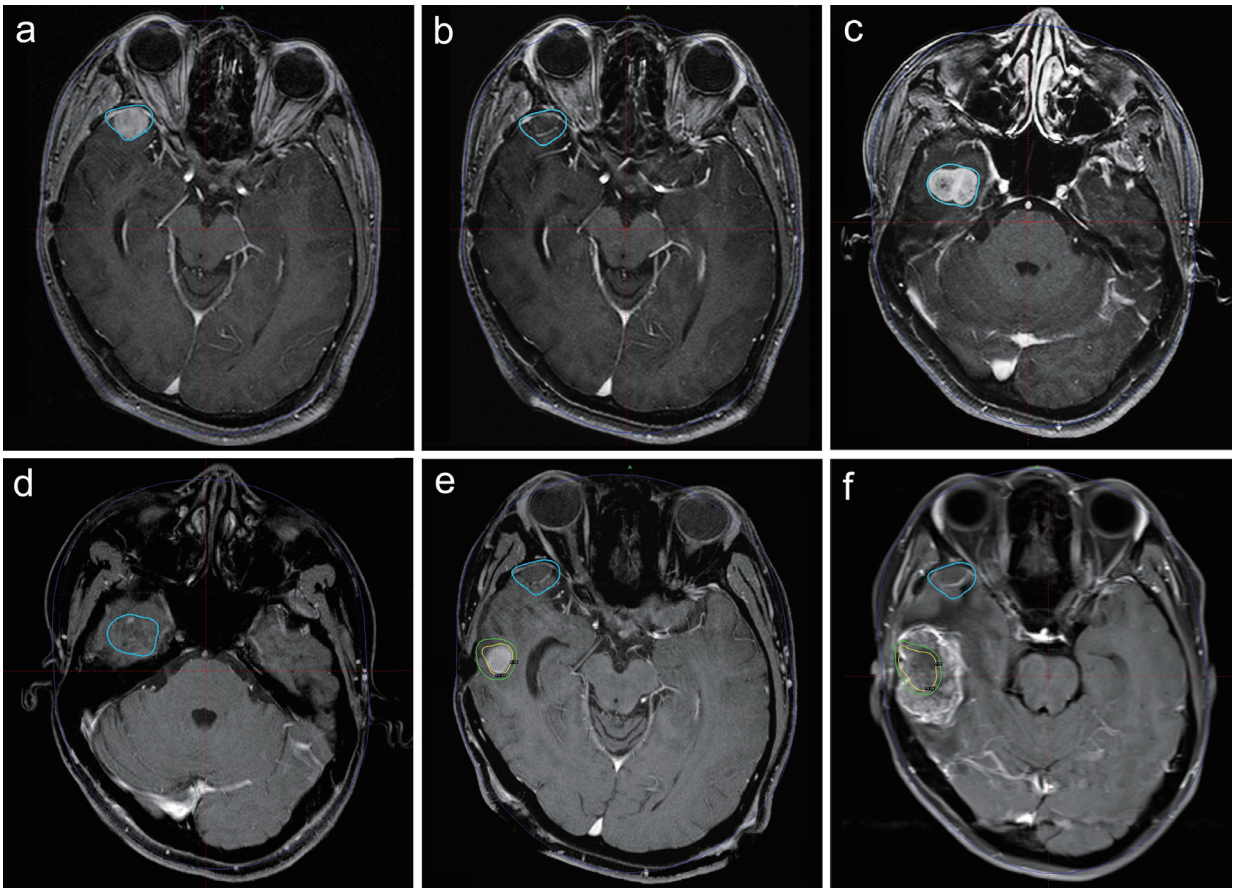

Fig. 3. This figure illustrates a patient who had previously undergone two resections and one EBRT before undergoing GKRS for two recurrences. (a) The prescription dose was 12 Gy, delivered to an isodose line of 50.0%. (b) At the six-month follow-up, the tumor shrank significantly. (c) However, a new tumor developed and was treated with a prescription dose of 14 Gy, delivered to the 52% isodose line using GKRS. (d) The second tumor shrank significantly at the 27-month follow-up after the initial GKRS. (e) Simultaneously, a new tumor was treated with the third GKRS at a prescription dose of 13 Gy, delivered to the 50% isodose line. (f) At the 35-month follow-up after the initial GKRS, the third tumor had increased in size, while the first tumor remained under control. EBRT, external beam radiotherapy; GKRS, gamma knife radiosurgery.

tients undergoing reoperation, five patients' tumors (28%) showed progression from grade 2 to grade 3. The median time from GKRS to grade 3 meningioma was 36 months (range: 6–100 months).

Discussion

Grade 2 meningiomas are aggressive neoplasms with high recurrence rates. They have significantly worse outcomes after either recurrence or subtotal resection, approximating those of grade 3 meningiomas.[11] SRS has also been increasingly used as an alternative therapeutic option to EBRT for patients with residual or recurrent grade 2 meningiomas.[8–10] In this series, we demonstrate that GKRS can achieve an acceptable five-year local control rate (65%) and PFS rate (44%), and most patients tolerated GKRS well, except for three (4%) patients who had previous EBRT or large tumors. Furthermore, none of the 23 patients who received repeated GKRS after initial GKRS developed symptomatic adverse radiation effects.

In previous literature, the PFS rates at five years for grade 2 meningiomas treated with radiosurgery ranged from 16% to 83%, and the outcomes varied widely (Table 4).[12–23] Grade 2 meningiomas represent a broad spectrum of tumors, and their biological behavior is highly heterogeneous. Due to this heterogeneity, small sample sizes can lead to large variances in results. Most previous studies consisted of relatively small sample sizes, which may partly account for this variance. Recently, a large multicenter study by Kowalchuk *et al*.[12] analyzed 233 patients with grade 2 meningiomas treated with radiosurgery and reported PFS rates of 53.9% and 33.1% at three and five years, respectively. Symptomatic radiation effects occurred in 6% of patients. Our study has a relatively large sample size comparable to that of a previous single-center study, and our results are consistent with those of the multicenter study.

The prospective phase II trial (RTOG 0539) investigated the outcomes of intensity modulated radiotherapy (IMRT) with a dose of 60 Gy for high-risk meningiomas (newly diagnosed or recurrent grade 3 meningiomas, recurrent grade 2, or newly diagnosed grade 2 meningiomas after subtotal resection). The authors reported a three-year PFS of 58.8%, which was similar to our series with a three-year PFS rate of 51.4%.[11] In our series, marginal recurrence was defined as new tumor formation outside the prescribed line but within the resection cavity. Our results showed high marginal recurrence comparable with IMRT (27/39 vs. 1/14). GKRS precisely delivers a high dose of radiation to the target and has a limited effect on outfield tissues. Considering the site of marginal recur-

Table 4. Literature summary of the main clinical studies on grade 2 meningioma treated with stereotactic radiosurgery

Author (year)	Number of patients	Dose (Gy)	Volume (cm^3)	Follow up (month)	Control rate (grade 2)
Harris *et al*.,2003[12]	II: 18	mean 14.9	mean 14.6	28	five-year PFS:83%
Kano *et al*.,2007[13]	II: 10 III: 2	mean 18	median 2.87	43	five-year PFS:48.3%
Attia *et al*.,2012[14]	II: 24	median 14	median 7.9	43	five-year PFS:25%
Pollock *et al*.,2012[15]	II: 37 III: 13	median 15	median 14.6	38	five-year PFS:40%
Hanakita *et al*.,2013[16]	II: 22	median 18	median 6	23.5	five-year PFS:16%
Aboukais *et al*.,2015[17]	II: 27	mean 15.2	mean 5.4	56.4	three-year LC:40%, three-year RC:33%
Wang *et al*.,2016[18]	II: 37 III: 9	median 12.5	median 11.7	32.6	three-year PFS:30.6%, five-year PFS:20.4%
Zhang *et al*.,2016[19]	II: 44	Median 20	median 3.33	28	three-year RC:58%, four- to five-year RC:58%
Reffat *et al*.,2017[20]	II: 75	mean 16	mean 3.5	41	five-year LC:55.7%
Kowalchuk *et al*.,2021[21]	II: 233	Median 15	median 4.74	37.6	three-year PFS:53.9%, five-year PFS:33.1%
Helis *et al*., 2020[22]	II, III: 48	Median 15	median 2.49	68.6	five-year DFS:47.2%
Our study	II: 70	median 13	median 3.9	48	three-year PFS:51%, five-year PFS:44%

II, III, World Health Organization grades II, III. DFS, disease-free survival; LC, local control; PFS, progression-free survival; RC, regional control.

rence, only marginal recurrence close to the prescribed line might be controlled by higher doses. Our analysis showed that margin dose was not associated with marginal recurrence. Valery *et al*.[23] also analyzed marginal recurrence in grade 2 meningiomas and observed only a trend toward better marginal control with higher doses. To decrease the possibility of marginal recurrence, enlargement of the target volume should be considered, especially for small lesions or surgical beds. Another option might be EBRT with an SRS boost. Helis *et al*.[22] reported six patients with grade 2 meningiomas who underwent SRS as a boost to EBRT. Of these six patients, none experienced marginal failure, and only one experienced local failure at the time of the last follow-up. However, two patients experienced severe complications after SRS. In our series, two of nine patients receiving prior EBRT had symptomatic radiation necrosis after GKRS. Given the heterogeneity of grade 2 meningiomas and radiation-related complications, we recommend SRS boosts in patients with risk factors associated with marginal recurrence. To reduce high-grade toxicity, Helis *et al*.[22] also proposed that the SRS boost should target the areas immediately adjacent to the tumor cavity without expansion. This strategy may be a promising treatment option, but further investigation is needed.

In previous literature, factors associated with tumor progression and overall survival included age, tumor location, tumor size, mitotic index, prescription dose, timing of treatment, prior RT, conformality index, multiple lesions, and multiple prior recurrences.[12–24] Among these factors, some reflect the aggressive nature of grade 2 meningiomas, while others are therapy-related parameters. Our results show that multiple lesions and multiple prior recurrences were significantly associated with worse PFS, marginal recurrence, and distant recurrence. Grade 2 meningiomas with these factors may represent inherently more aggressive lesions. Chen *et al*.[24] reported 65 patients with atypical meningiomas who received salvage therapy, including surgery, RT alone, and surgery with adjuvant RT. They found that multifocal recurrences and more previous recurrences were associated with further progression. Helis *et al*.[22] identified 48 patients who had 183 high-grade meningiomas treated with SRS and found that distant recurrences were significantly more common in patients with multiple lesions treated in a single SRS session. Several studies have demonstrated a positive correlation between increased dosage and enhanced tumor control. The recommended minimum doses are 12–18 Gy.[15,17,19,23] Meng *et al*.[25] recently reported 88 patients who underwent GKRS for grade 2 meningiomas in a single session and found that for tumors with Ki-67 > 10%, a margin dose of ≥14 Gy showed significantly better tumor control, but this was not the case for tumors with Ki-67 ≤ 10%. Our multivariate analysis indicated that a marginal dose of ≤13 Gy independently predicts local recurrence. The high-dose group demonstrated higher rates of local control (≥14 Gy: 86% at three years vs. ≤13 Gy: 64% at three years). We suggest that higher doses should be applied to achieve better local control. However, high-dose therapy may present challenges in certain situations, such as proximity to critical structures, prior radiotherapy, and large tumor sizes. Hypofractionated stereotactic radiosurgery has been utilized for large tumors or those close to critical structures due to its potential advantages. Marchetti *et al*.[26] analyzed 24 patients with grade 2 meningiomas treated with multisession radiosurgery and reported a three-year PFS of 47%, a local control rate of 86%, and an adverse radiation effect rate of 4%. However, additional investigations are needed to confirm the long-term outcomes of hypofractionated stereotactic radiosurgery for grade 2 meningiomas.

The optimal timing of GKRS is not well established. Our results show that patients receiving salvage therapy for tumors at multiple recurrences had significantly worse outcomes than those receiving adjuvant therapy for residual tumors after initial surgery or salvage therapy for tumors at first recurrence. Because multiply recurrent meningiomas are more aggressive, a comparison between patients receiving SRS after initial resection and those receiving SRS at first recurrence is appropriate to evaluate the optimal timing of SRS. In our subgroup analysis, there was no significant difference in overall survival or tumor control between adjuvant therapy for residual tumors after initial surgery and salvage therapy for tumors at first recurrence. However, large tumor volumes, associated with worse PFS, have been reported in previous series.[15,16,21] The enlargement of the tumor may lead to lower prescription doses and increased morbidity. Therefore, we suggest that residual tumors should be treated aggressively within a short interval.

This study was retrospective and had its limitations. Rigorous

analysis of radiation-related complications was particularly difficult because many patients experienced multiple relapses and repeated treatments. However, based on clinical and radiographic findings, the assessment of severe radiation-related complications was reliable. Future directions to improve the treatment of grade 2 meningiomas may stem from recent advancements in next-generation sequencing, which may better distinguish the heterogeneity of grade 2 meningiomas. Molecular classification of meningiomas can more accurately reflect the biological behavior of the tumor and improve the selection of treatment parameters.

Conclusions

Our results support the use of GKRS as a reasonable treatment option in the management of grade 2 meningiomas. A higher margin dose should be considered to achieve better local control. Outfield progression (marginal and/or distant recurrence) was common, particularly in patients with multiple prior recurrences and/or multiple lesions. More aggressive treatment strategies should be explored for patients with these risk factors.

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Conflict of interest

Dr. Shibin Sun has been serving as an executive associate editor of *Neurosurgical Subspecialties* since July 2024. The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this article. Additionally, the authors declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Author contributions

Conceptualization (EB, KW, DG, BL, AL, SS), methodology, software, validation, form analysis, investigation, resources, data curation (EB, KW), writing - original draft (EB), writing - review & editing (KW, DG, BL, AL, SS), supervision, and project administration (SS). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study was carried out in accordance with the recommendations of the Declaration of Helsinki (as revised in 2013). This study was approved by Beijing Tiantan Hospital institutional review board (Approval No. KY2020-135-01). The individual consent for this retrospective analysis was waived.

Data sharing statement

The dataset used in support of the findings of this study are available from the corresponding author at ssbwyl@vip.sina.com upon request.

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