

Comparison of outcomes of gamma knife radiosurgery for secondary and de novo grade 2 meningiomas: a single-center retrospective study

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Abstract

Objective

The purpose of this study was to compare outcomes between secondary and de novo grade 2 meningiomas undergoing Gamma Knife radiosurgery (GKRS).

Methods

Eighteen patients, including secondary grade 2 meningioma group ($n = 6$) and de novo grade 2 meningioma group ($n = 12$), treated with GKRS were enrolled in this single-center retrospective study.

Results

The median tumor volume was 23.4 (range, 5.5–104.0) ml and 9.4 (range, 0.4–24.9) ml in secondary and de novo grade 2 meningioma group respectively ($p = 0.061$). Ten patients (55.6%) experienced radiological progression with a median follow-up time of 35.7 (range, 9.4–138.2) months. The median time to radiological progression was 34.5 (range, 14.5–97.7) months. The radiological progression-free survival (PFS) was 74%, 55%, and 15% at 2, 3 and 5 years respectively. The radiological PFS at 2 and 3 years was 60% and 20%, 82% and 82% in secondary and de novo grade 2 group respectively. Secondary grade 2 meningiomas were significantly related with poorer radiological PFS in univariate analysis ($p = 0.021$). Nine patients (50%) occurred clinical progression in the study, including headache ($n = 7$), cranial nerve dysfunction ($n = 5$), seizure ($n = 1$) and extremity weakness ($n = 1$). Secondary grade 2 meningiomas were significantly related with clinical progression in univariate analysis ($p = 0.045$).

Conclusions

Secondary grade 2 meningiomas had a shorter radiological and clinical PFS after GKRS than de novo grade 2 meningiomas. Secondary grade 2 meningiomas were an independent risk factor for poor prognosis after GKRS.

Introduction

Meningiomas are the most common primary intracranial tumor, accounting for nearly 37.6% of all intracranial tumors¹. Almost 17.7% of meningiomas with documented WHO grade are grade 2¹. As malignant gliomas, Meningiomas can progress from benign to atypical or anaplastic variants^{2,3}. It is estimated that 20%-40% of meningiomas are secondary tumors which originated from grade 1 meningiomas⁴⁻⁶. As a consequent, grade 2 meningiomas are categorized as secondary or de novo tumors⁷.

Up to now, the treatment for grade 2 meningiomas is challengeable. Surgical resection is still the first choice⁸. Maximal surgical resection is the most important factor related with prediction of prognosis. However, these tumors can demonstrate a higher tumor recurrent rate and poor prognosis despite gross total resection, because of its heterogeneity and unpredictable behavior^{9–11}. The recurrence of meningiomas can cause significant mortality and morbidity. Thus, in order to reduce tumor recurrence, great effort should be made in the management of grade 2 meningiomas.

Gamma knife radiosurgery (GKRS), which can provide a favorable tumor control rate and has advantages of better dose conformity, a less invasive treatment, a highly focused and precise delivery of radiation in a single session, is widely used for postoperative residual or recurrent grade 2 meningiomas. Previous studies have reported stereotactic radiosurgery (SRS) could offer a 3-year tumor control rate of 19%-74% for grade 2 meningiomas^{12–17}.

However, the differences between secondary and de novo grade 2 meningiomas are still unclear. As secondary meningiomas have already undergone surgical resection at least once and/or radiotherapy, they may behave differently and have different prognosis. According to the studies by Zhao et al¹⁸ and Champeaux et al⁴, secondary grade 2 meningiomas had a much shorter surgical recurrence-free survival and overall survival. Because of its rarity, the prognosis of secondary grade 2 meningiomas treated with GKRS are poorly understood. Therefore, in order to compare outcomes between secondary and de novo grade 2 meningiomas undergoing GKRS, we conducted a single-center retrospective study.

Methods

Patient selection

Between December 2008 and December 2017, 6 cases of secondary grade 2 meningiomas (Fig. 1) and 12 cases of de novo grade 2 meningiomas (Fig. 2) who had complete clinical data and at least once follow-up in our center were retrospectively reviewed. All of the 6 secondary meningiomas had undergone at least twice surgical resection and GKRS in our center. All of the 12 cases of de novo grade 2 meningiomas were residual tumors after the primary treatment of surgery. All of the histological tissue specimens had been confirmed by an experienced pathologist according to the 2016 WHO classification. This retrospective study was approved by the institutional committee of the Second Affiliated Hospital of Guangzhou Medical University.

Radiological and clinical evaluations

All of these patients were usually followed up with radiological and clinical evaluation every 6 months for the first 3 years and thereafter yearly. Tumor volume was calculated using the following formula: $V = \text{anteroposterior diameter} \times \text{horizontal diameter} \times \text{vertical diameter} \times \pi/6$ ¹⁹. Tumors shrinking at least 10% in volume was considered shrinkage. Tumor changing within 10% in volume was considered stable. Tumor enlarging at least 10% in volume was considered progression²⁰.

Radiosurgical techniques

Leksell B-type Gamma Knife radiosurgery (Elekta Instruments, Inc, Stockholm, Sweden) was used for these meningioma patients before April 2014 and Perfexion thereafter. After the placement of Leksell stereotactic frame G, stereotactic contrast-enhanced MRI was performed to obtain MRI image for delineating target. GKRS treatment plan was proposed according to experienced neurosurgeons, medical physicist and radiation oncologists.

Statistical analysis

The comparison of means of continuous variables with normal distribution was performed by independent-sample t test. Wilcoxon rank sum test was used for continuous variables with abnormal distribution. Analysis of categorical variables was performed by Chi-square test and Fisher exact test. Log-rank test statistics and Cox proportional hazard models were used for univariate analysis and multivariate analysis respectively. Kaplan-Meier curves were plotted for progression-free survival. Probability values < 0.05 were considered statistically significant. For statistical analysis, IBM's SPSS (version 21.0) was used.

Results

Baseline and treatment characteristics

The population in this study consisted of 18 patients, including secondary grade 2 meningioma group (n = 6) and de novo grade 2 meningioma group (n = 12). There were 2 (33.3%) and 8 (66.7%) male patients in secondary and de novo grade 2 meningioma group respectively. There were 6 (50%) non-skull base tumors in de novo grade 2 meningioma group. All of tumors were skull base in secondary grade 2 meningioma group. All the patients had undergone at least once surgical resection in de novo grade 2 meningioma group and at least twice surgical resection in secondary grade 2 meningioma group. The median follow-up was 58.0 (range, 25.5-106.7) months and 29.9 (range, 9.4-138.3) months in secondary and de novo grade 2 meningioma group respectively. The median time to malignant transformation in secondary grade 2 meningioma group was 150.3 (range, 35.0-177.2) months. All of the tumors had undergone GKRS treatment before malignant transformation in secondary grade 2 meningioma group. The median tumor volume, age, margin dose, prescription isodose and max dose were 23.4 ml, 51.8 years, 14.5 Gy, 50%, 30 Gy, and 9.4 ml, 54.5 years, 13.5 Gy, 45%, 32.5 Gy in the secondary and do novo grade 2 meningioma group respectively. All of the treatment and baseline characteristics were similar in the two groups. (Table 1)

Table 1
Baseline and treatment characteristics of the study group.

Characteristic	Secondary grade 2 meningiomas	De novo grade 2 meningiomas	P value
No. of patients	6 (33.3)	12 (66.7)	NA
Male, n (%)	2 (33.3)	8 (66.7)	0.321
Median age, (range), years	51.8 (42.3–60.0)	54.5 (26.5–64.1)	0.921
Median tumor volume at GKRS, (range), ml	23.4 (5.5–104.0)	9.4 (0.4–24.9)	0.061
Median FU duration, (range), months	58.0 (25.5-106.7)	29.9 (9.4-138.3)	0.092
Non-skull base tumors, n (%)	0	6 (50)	0.054
No. of surgery, n (%)			
Once	NA	10 (83.3)	NA
Twice	5 (83.3)	2 (16.7)	NA
Three times	1 (16.7)	NA	NA
Tumor histology, n			
Atypical	5 (83.3)	8 (66.7)	NA
Chordoid	1 (16.7)	2 (16.7)	NA
Clear cell	0	2 (16.7)	NA
Median time to malignant transformation, (range), months	150.3 (35.0-177.2)	NA	NA
Prior GKRS	6 (100)	0	NA
Median margin dose, (range), Gy	14.5 (13.0–15.0)	13.5 (12.0–15.0)	0.395
Median maximum dose, (range), Gy	30.0 (26.0–33.0)	32.5 (24.0-32.5)	0.506
Median prescription isodose, (range), %	50 (40–50)	45 (40–50)	0.176
Abbreviations: FU, follow up; GKRS, gamma knife radiosurgery; NA, not available.			

Treatment outcomes after GKRS

Ten patients (55.6%) experienced radiological progression with a median follow-up time of 35.7 (range, 9.4-138.2) months. The median time to radiological progression was 34.5 (range, 14.5–97.7) months. The radiological progression-free survival (PFS) was 74%, 55%, and 15% at 2, 3 and 5 years respectively (Fig. 3A). There were 5 (83.3%) and 5 (41.7%) patients with tumor progression in secondary and de novo grade 2 meningioma group respectively (Table 2). The median time to radiological progression was 31.4

(range, 22.4–41.3) months and 48.9 (range, 14.5–97.7) months in secondary and de novo grade 2 meningioma group respectively. The radiological PFS at 2 and 3 years was 60% and 20%, 82% and 82% in secondary and de novo grade 2 meningioma group respectively. Secondary grade 2 meningiomas were significantly associated with poorer radiological PFS in univariate analysis ($p = 0.021$) (Fig. 3B) (Table 3).

Table 2
GKRS treatment outcomes in the entire series.

Outcomes	Secondary grade 2 meningiomas, n (%)	De novo grade 2 meningiomas, n (%)
Radiological outcomes		
Tumor control	1 (16.7)	7 (58.3)
Tumor shrinkage	0	7 (58.3)
Stable tumor	1 (16.7)	0
Progression	5 (83.3)	5 (41.7)
Clinical progression	5 (83.3)	4 (33.3)
CN dysfunction	5 (83.3)	0
II	5 (83.3)	0
III/IV/VI	1 (16.7)	0
V	1 (16.7)	0
Headache	3 (50)	4 (33.3)
Seizure	1 (16.7)	0
Extremity weakness	0	1 (8.3)
Abbreviations: CN, cranial nerve.		

Table 3
Univariate and multivariate Cox proportional hazards regression analyses for radiological progression, and clinical progression in the entire series.

Characteristics	Radiological progression	Clinical progression
	Univariate, <i>p</i>	Univariate, <i>p</i>
Age ≥ 55y	0.096	0.196
Gender	0.911	0.539
Tumor volume ≥ 10 ml	0.566	0.343
Non-skull base tumors	0.763	0.529
Margin dose < 15Gy	0.620	0.527
Maximum dose ≤ 32Gy	0.787	0.773
Secondary grade 2 meningiomas	0.021	0.045
*Statistically significant ($P < 0.05$).		
Boldface type indicates statistical significance.		

Nine patients (50%) occurred clinical progression in the study, including headache (n = 7), cranial nerve dysfunction (n = 5), seizure (n = 1) and extremity weakness (n = 1) (Table 2). The median time to clinical progression was 34.8 (range, 15.8–72.2) months. There were 5 (83.3%) and 4 (33.3%) patients occurring clinical progression in secondary and de novo grade 2 meningioma group respectively. Secondary grade 2 meningiomas were related with clinical progression in univariate analysis ($p = 0.045$) (Fig. 4) (Table 2).

Discussion

Surgery is the first choice in the management of grade 2 meningiomas. However, grade 2 meningiomas are a heterogeneous group of histologically aggressive tumors, with a high incidence of tumor recurrence and progression as compared to benign meningiomas. Therefore, treatment options for tumor recurrence and progression include repeat surgery and radiotherapy. Given the increased morbidity and poor quality of life after repeat surgical resection²¹, postoperative radiotherapy is advocated in the management of postoperative residual or recurrent grade 2 meningiomas.

Radiotherapy for grade 2 meningiomas

Although adjuvant radiotherapy for atypical meningiomas after gross total resection is still on controversial, it could significantly improve tumor control rate after subtotal resection²². Mair et al²³ analyzed 114 cases of grade 2 atypical meningiomas diagnosed using 2000 WHO criteria, and reported a significant benefit after radiotherapy after subtotal resection. In the study of Jo K et al²⁴, for atypical

meningiomas with incomplete resection, the median interval to tumor recurrence increased from 17 months for surgery alone to 39 months for adjuvant radiotherapy.

SRS and fractionated external beam radiotherapy (fEBRT) are both reasonable options for postoperative residual or recurrent grade 2 meningiomas. Previous studies have reported SRS and fEBRT could offer a 3-year tumor control rate of 19%-74%¹²⁻¹⁷ and 45%-71%^{12, 17, 25} for grade 2 meningiomas respectively. However, studies did not find significant difference in tumor control between fEBRT and SRS^{17, 26}. As SRS has the advantage of a highly precise, better dose conformity, minimizing radiation dose to surrounding tissues and shorter duration of treatments, it seems more attractive than fEBRT.

Tumor control after SRS and related risk factors

Tumor control after SRS and related risk factors have been reported in the literatures. In the study of Choi et al¹³, 25 cases of residual or recurrent atypical meningiomas treated with SRS with a median marginal dose of 22 Gy (range, 16–30) in 1 to 4 fractions, the 3-year local control rate was 74%, the number of recurrences before SRS, late SRS and age at treatment ≥ 60 years were associated with recurrence after SRS on univariate analysis. In the study of Ferraro et al²⁷, 31 cases of atypical meningiomas were treated with GKRS, the median time to recurrence was 27.5 months, the 3-year PFS was 70.1%, margin dose was the only significant factor related with recurrence in multivariate analysis. In the study of Pollock et al¹⁴, 50 cases of grade 2 (= 37) and 3 (n = 13) treat with SRS with a median margin dose of 15 Gy. The 5-year PFS was 40%. In patients who failed prior EBRT, the 3-year PFS was 19%. Having failed EBRT was a negative predictor of PFS. In the study of Kano et al¹⁵, the authors found the 5-year PFS in lesions treated with SRS below 20 Gy and 20 Gy were 29.4% and 63.1% respectively. The marginal dose < 20 Gy was a significant factor for PFS in high-grade meningiomas treated with SRS. Aboukais et al¹⁶ reported 27 cases of grade 2 meningiomas treated with SRS with a median margin dose of 15.2 (range, 12–21) Gy, the 3-year local control was 40%. Age and tumor volume were significantly related with local tumor control in univariate analysis.

In the current study, because some tumors were close to optic chiasm and optic nerve or due to the large tumor volume, the median margin dose was 14.5 Gy and 13.5 Gy in secondary and de novo grade 2 meningioma group respectively, which might be a little lower than other studies. The radiological PFS was 74% and 55% at 2 and 3 years respectively, which was similar with other studies. The median time to radiological progression was shorter in secondary grade 2 meningioma group than de novo grade 2 meningioma group (31.4 vs 48.9 months), secondary grade 2 meningiomas were significantly related with poorer prognosis. Meningiomas with multiple recurrences and prior treatment failures are considered more aggressive and difficult to treat. However, in the current study, all of the secondary grade 2 meningiomas had at least twice surgery failures and GKRS treatment failure and were more aggressive and resistant to radiation than those de novo grade 2 meningiomas. Besides, there was no radiation-naïve patient in the secondary grade 2 meningioma group. Therefore, this could be a source of bias. Up to now, there was no standard treatment for secondary grade 2 meningiomas. Due to its poor prognosis, higher radiation dose might be helpful for better tumor control.

Secondary grade 2 meningiomas

Malignant transformation is not an uncommon phenomenon in benign meningiomas. It is estimated that 20%-40% of meningiomas are secondary tumors which originated from grade 1 meningiomas⁴⁻⁶. As stepwise genetic progression involving in malignant transformation^{3, 28, 29}, secondary and de novo grade 2 meningiomas may behave differently. Recent studies indicated secondary meningiomas were associated with poor PFS and overall survival. In the study of Zhao et al¹⁸, 89 cases of atypical meningiomas were reviewed. Total resection was achieved in 80.9%. Forty (44.9%) patients underwent radiotherapy after surgery. Patients with secondary atypical meningiomas showed a threefold increased risk of recurrence. Secondary atypical meningiomas were related with poor PFS on multivariate analysis. In the study of Champeaux et al⁴, 194 patients with grade 2 meningiomas were reviewed. Thirty-one patients (16%) had a previous history of grade 1 meningiomas. These patients underwent a total of 344 surgical resections and 43.3% received radiotherapy. Secondary grade 2 meningiomas were related with the surgical recurrence-free survival and overall survival. In these studies, only a part of patients underwent radiotherapy for secondary meningiomas. There was no study comparing the outcomes between secondary and de novo grade 2 meningiomas undergoing GKRS.

In the current study, we did not investigate molecular markers in this study. CDKN2A/B and TERT promoter have been associated with meningioma behavior and poor prognosis^{30, 31}. The 2021 WHO classification system indicates any meningioma with CDKN2A/B homozygous deletion and/or TERT promoter mutation is allotted to grade 3, irrespective of histological criteria of anaplasia⁸. Thus, future study needed to investigate molecular markers and genetic signatures associated with malignant transformation and prognosis.

Study limitations

Although this was the first study comparing outcomes between secondary and de novo grade 2 meningiomas undergoing GKRS, there were several limitations in the study. First, it was a single-center retrospective study with selection and treatment biases. Second, because of the rare incidence of secondary meningiomas, only 6 cases of secondary grade 2 meningiomas treated with GKRS were included in this study. The statistical power was limited by the number of cases in the study. Third, the pathological diagnosis was not based on the 2021 WHO classification system. The information of molecular markers was not available in this study. Finally, there was no radiation-naïve patient in the secondary grade 2 meningioma group. This could be a source of bias.

Conclusions

In this single-center retrospective study, we found secondary grade 2 meningiomas had a shorter radiological and clinical PFS after GKRS than de novo grade 2 meningiomas. The radiological PFS at 3 years was 20% and 82% in secondary and de novo grade 2 group respectively. Secondary grade 2 meningiomas were an independent risk factor for poor prognosis after GKRS. Therefore, further

prospective studies should be carried out to investigate the outcomes of GKRS for secondary and de novo grade 2 meningiomas.

Abbreviations

fEBRT
fractionated external beam radiotherapy
GRKS
Gamma Knife radiosurgery
PFS
progression-free survival
SRS
stereotactic radiosurgery

Declarations

Acknowledgements

Not applicable.

Declaration of interest

Declarations of interest: none.

Author contribution

Dili Song, Guangxin Hu and Liping Shen made research idea and designed study; Zijing Wang, Jiaming Fu and Lin Chen collected data; Xiaomin Zhou and Xinwu Liu analyzed the data; Dili Song, Jiaming Fu and Jinxiu Yu wrote the paper; Yongguang Cai and Junyi Fu revised the paper.

Consent for publication

Each author contributed important content during manuscript drafting or revision and accepts accountability for the overall work, and all the authors agreed on the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to part of the data in the study related to other studies, but are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the institutional committee of the Second Affiliated Hospital of Guangzhou Medical University. The patients/ participants provided their written informed consent to participate in this study. All procedures performed were in accordance with the ethical standards of these committees and with the 1964 Declaration of Helsinki and its later amendments.

Competing interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

References

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. *Neurooncology*. 2019;21(Suppl 5):v1–100. <https://doi.org/10.1093/neuonc/noz150>.
2. Jaaskelainen J. Seemingly complete removal of histologically benign intracranial meningioma: late recurrence rate and factors predicting recurrence in 657 patients. A multivariate analysis. *Surg Neurol*. 1986;26(5):461–9. [https://doi.org/10.1016/0090-3019\(86\)90259-4](https://doi.org/10.1016/0090-3019(86)90259-4).
3. Al-Mefty O, Kadri PA, Pravdenkova S, Sawyer JR, Stangeby C, Husain M. Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. *J Neurosurg*. 2004;101(2):210–8. <https://doi.org/10.3171/jns.2004.101.2.0210>.
4. Champeaux C, Wilson E, Shieff C, Khan AA, Thorne L. WHO grade II meningioma: a retrospective study for outcome and prognostic factor assessment. *J Neurooncol*. 2016;129(2):337–45. <https://doi.org/10.1007/s11060-016-2181-2>.
5. Champeaux C, Jecko V, Houston D, et al. Malignant Meningioma: An International Multicentre Retrospective Study. *Neurosurgery*. 2019;85(3):E461–9. <https://doi.org/10.1093/neuros/nyy610>.
6. Yang SY, Park CK, Park SH, Kim DG, Chung YS, Jung HW. Atypical and anaplastic meningiomas: prognostic implications of clinicopathological features. *J Neurol Neurosurg Psychiatry*. 2008;79(5):574–80. <https://doi.org/10.1136/jnnp.2007.121582>.
7. Harmanci AS, Youngblood MW, Clark VE, et al. Integrated genomic analyses of de novo pathways underlying atypical meningiomas. *Nat Commun*. 2017;8:14433. <https://doi.org/10.1038/ncomms14433>.

8. Goldbrunner R, Stavrinou P, Jenkinson MD et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro-oncology*. 2021. <https://doi.org/10.1093/neuonc/noab150>
9. Stark AM, Buhl R, Mehdorn HM. Early gross recurrence of atypical meningioma. *J Neurooncol*. 2005;75(2):223–4. <https://doi.org/10.1007/s11060-005-2117-8>.
10. Jenkinson MD, Waqar M, Farah JO, et al. Early adjuvant radiotherapy in the treatment of atypical meningioma. *J Clin neuroscience: official J Neurosurgical Soc Australasia*. 2016;28:87–92. <https://doi.org/10.1016/j.jocn.2015.09.021>.
11. Pereira BJA, de Almeida AN, Paiva WS, Teixeira MJ, Marie SKN. Impact of radiotherapy in atypical meningioma recurrence: literature review. *Neurosurg Rev*. 2019;42(3):631–7. <https://doi.org/10.1007/s10143-018-0959-8>.
12. Chen WC, Hara J, Magill ST, et al. Salvage therapy outcomes for atypical meningioma. *J Neurooncol*. 2018;138(2):425–33. <https://doi.org/10.1007/s11060-018-2813-9>.
13. Choi CY, Soltys SG, Gibbs IC, et al. Cyberknife stereotactic radiosurgery for treatment of atypical (WHO grade II) cranial meningiomas. *Neurosurgery*. 2010;67(5):1180–8. <https://doi.org/10.1227/NEU.0b013e3181f2f427>.
14. Pollock BE, Stafford SL, Link MJ, Garces YI, Foote RL. Stereotactic radiosurgery of World Health Organization grade II and III intracranial meningiomas: treatment results on the basis of a 22-year experience. *Cancer*. 2012;118(4):1048–54. <https://doi.org/10.1002/cncr.26362>.
15. Kano H, Takahashi JA, Katsuki T, et al. Stereotactic radiosurgery for atypical and anaplastic meningiomas. *J Neurooncol*. 2007;84(1):41–7. <https://doi.org/10.1007/s11060-007-9338-y>.
16. Aboukais R, Zairi F, Lejeune JP, et al. Grade 2 meningioma and radiosurgery. *J Neurosurg*. 2015;122(5):1157–62. <https://doi.org/10.3171/2014.9.JNS14233>.
17. Momin AA, Shao J, Soni P, et al. Outcomes of salvage radiation for recurrent world health organization grade II meningiomas: a retrospective cohort study. *J Neurooncol*. 2021;152(2):373–82. <https://doi.org/10.1007/s11060-021-03711-z>.
18. Zhao P, Hu M, Zhao M, Ren X, Jiang Z. Prognostic factors for patients with atypical or malignant meningiomas treated at a single center. *Neurosurg Rev*. 2015;38(1):101–7. <https://doi.org/10.1007/s10143-014-0558-2>. discussion 107.
19. Ge Y, Liu D, Zhang Z, et al. Gamma Knife radiosurgery for intracranial benign meningiomas: follow-up outcome in 130 patients. *NeuroSurg Focus*. 2019;46(6):E7. <https://doi.org/10.3171/2019.3.FOCUS1956>.
20. Pou P, Biau J, Verrelle P, et al. Long-Term Outcomes After Linac Radiosurgery for Benign Meningiomas. *Clin Oncol (R Coll Radiol (G B))*. 2020;32(7):452–8. <https://doi.org/10.1016/j.clon.2020.02.006>.
21. Poon MT, Fung LH, Pu JK, Leung GK. Outcome comparison between younger and older patients undergoing intracranial meningioma resections. *J Neurooncol*. 2013;114(2):219–27. <https://doi.org/10.1007/s11060-013-1173-8>.

22. Kaur G, Sayegh ET, Larson A, et al. Adjuvant radiotherapy for atypical and malignant meningiomas: a systematic review. *Neurooncology*. 2014;16(5):628–36. <https://doi.org/10.1093/neuonc/nou025>.
23. Mair R, Morris K, Scott I, Carroll TA. Radiotherapy for atypical meningiomas. *J Neurosurg*. 2011;115(4):811–9. <https://doi.org/10.3171/2011.5.JNS11112>.
24. Jo K, Park HJ, Nam DH, et al. Treatment of atypical meningioma. *J Clin neuroscience: official J Neurosurgical Soc Australasia*. 2010;17(11):1362–6. <https://doi.org/10.1016/j.jocn.2010.03.036>.
25. Rogers CL, Won M, Vogelbaum MA, et al. High-risk Meningioma: Initial Outcomes From NRG Oncology/RTOG 0539. *Int J Radiat Oncol Biol Phys*. 2020;106(4):790–9. <https://doi.org/10.1016/j.ijrobp.2019.11.028>.
26. Sun SQ, Cai C, Murphy RK, et al. Radiation Therapy for Residual or Recurrent Atypical Meningioma: The Effects of Modality, Timing, and Tumor Pathology on Long-Term Outcomes. *Neurosurgery*. 2016;79(1):23–32. <https://doi.org/10.1227/NEU.0000000000001160>.
27. Ferraro DJ, Funk RK, Blackett JW, et al. A retrospective analysis of survival and prognostic factors after stereotactic radiosurgery for aggressive meningiomas. *Radiation Oncol (London England)*. 2014;9:38. <https://doi.org/10.1186/1748-717X-9-38>.
28. Ketter R, Henn W, Niedermayer I, et al. Predictive value of progression-associated chromosomal aberrations for the prognosis of meningiomas: a retrospective study of 198 cases. *J Neurosurg*. 2001;95(4):601–7. <https://doi.org/10.3171/jns.2001.95.4.0601>.
29. Perez-Magan E, Rodriguez de Lope A, Ribalta T, et al. Differential expression profiling analyses identifies downregulation of 1p, 6q, and 14q genes and overexpression of 6p histone cluster 1 genes as markers of recurrence in meningiomas. *Neurooncology*. 2010;12(12):1278–90. <https://doi.org/10.1093/neuonc/noq081>.
30. Sievers P, Hielscher T, Schrimpf D, et al. CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. *Acta Neuropathol*. 2020;140(3):409–13. <https://doi.org/10.1007/s00401-020-02188-w>.
31. Maier AD, Stenman A, Svahn F, et al. TERT promoter mutations in primary and secondary WHO grade III meningioma. *Brain Pathol*. 2021;31(1):61–9. <https://doi.org/10.1111/bpa.12892>.

Figures

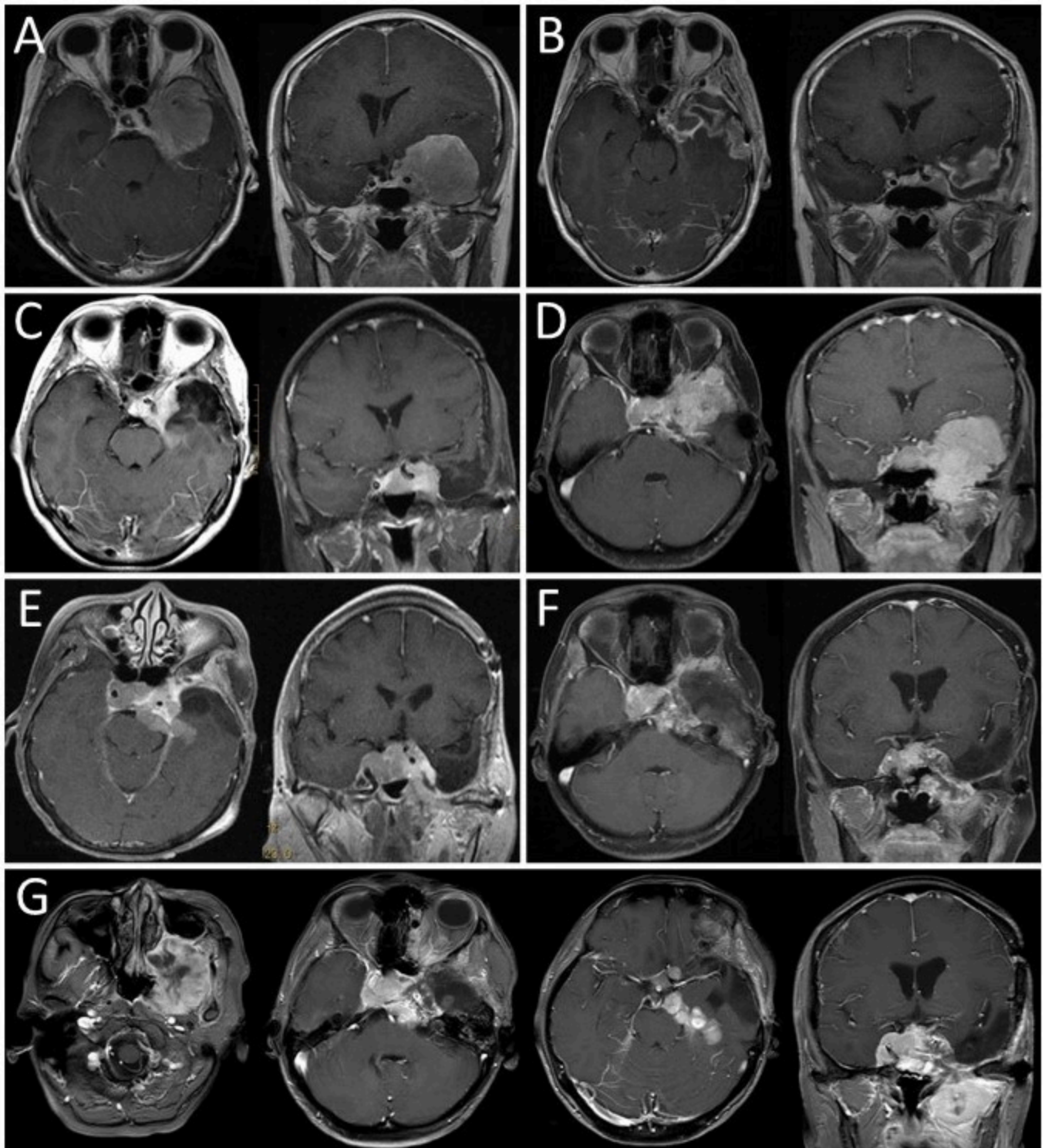


Figure 1

A 53.8-year-old female patient underwent adjuvant GKRS (margin dose, 12 Gy; maximum dose, 30 Gy) for parasellar grade 1 meningioma. The patient was diagnosed of secondary grade 2 meningioma by repeat surgical resection for tumor progression at 63.9 months after prior surgery. Finally, the patient occurred tumor progression at 31.7 months after repeat GKRS (margin dose, 13.2 Gy; maximum dose, 33 Gy). **A.** Contrast-enhanced T1-weighted MRI scans showed parasellar tumor. **B.** The patient underwent subtotal resection and was diagnosed of meningothelial meningioma. **C.** Postoperative GKRS for residual grade 1

meningioma at 22.4 months after surgical resection. **D.** MRI showed tumor progression at 41.1 months after GKRS. **E.** The patient underwent repeat GKRS for atypical meningioma confirmed by repeat surgical resection. **F.** MRI showed stable tumor at 22.4 months after repeat GKRS. **G.** MRI showed tumor progression at 31.7 months after repeat GKRS.

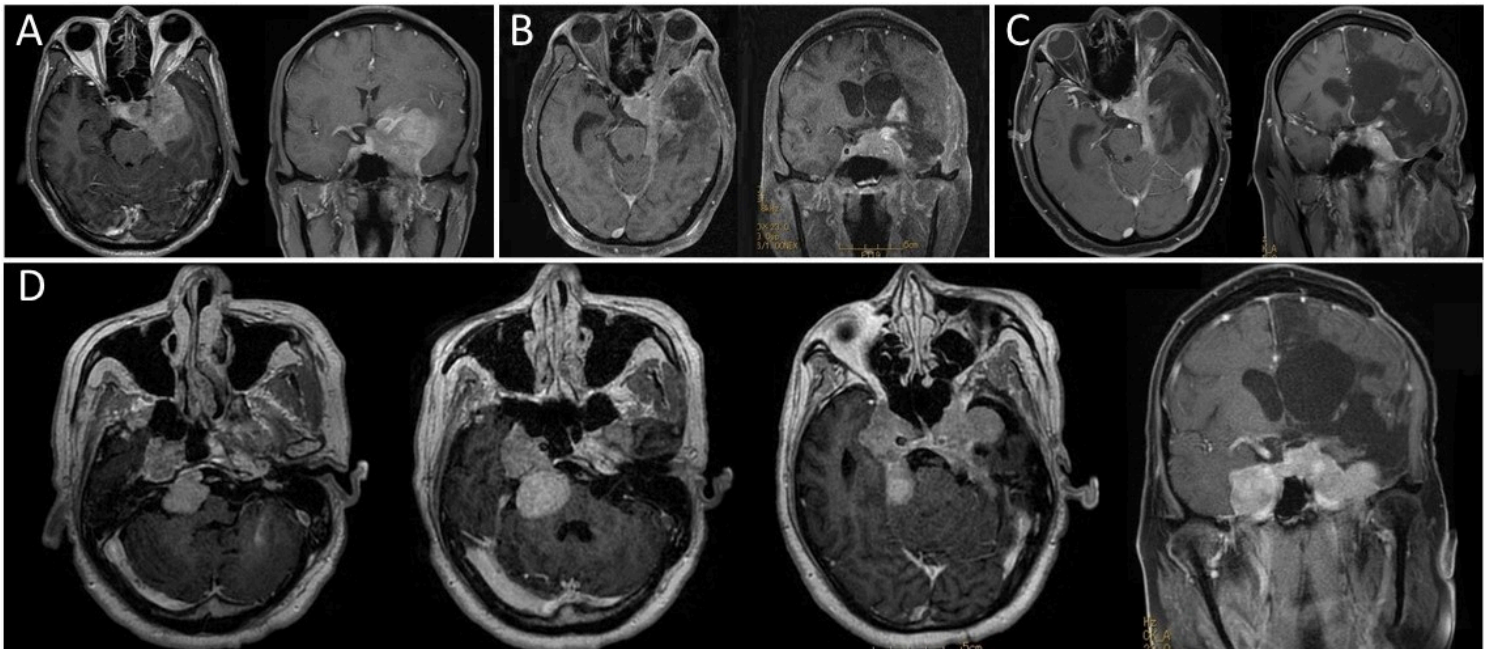


Figure 2

A 52.8-year-old male patient with parasellar de novo grade 2 meningioma underwent GKRS (margin dose, 12 Gy; maximum dose, 24 Gy) as adjuvant treatment for residual tumor after surgical resection. The patient developed tumor progression at 59.2 months after GKRS. **A.** Contrast-enhanced T1-weighted MRI scans showed parasellar tumor. **B.** Adjuvant GKRS for residual de novo grade 2 meningioma at 6.7 months after surgical resection. **C.** MRI showed stable tumor at 37.1 months after GKRS. **D.** MRI showed tumor progression at 59.2 months after GKRS.

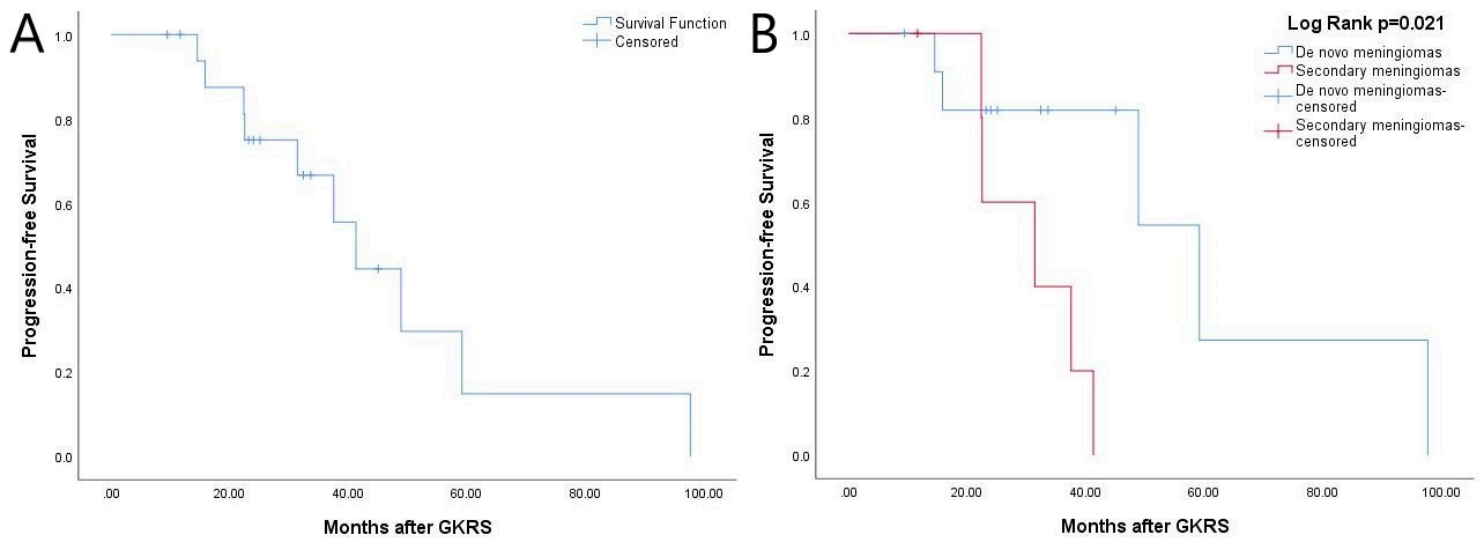


Figure 3

A. Kaplan-Meier curve of radiological PFS in the entire series. The PFS was 100%, 74%, 55%, 29%, and 15% at 1, 2, 3, 4, and 5 years. **B.** Kaplan-Meier curve of radiological PFS of secondary VS de novo grade 2 meningiomas ($p=0.021$).

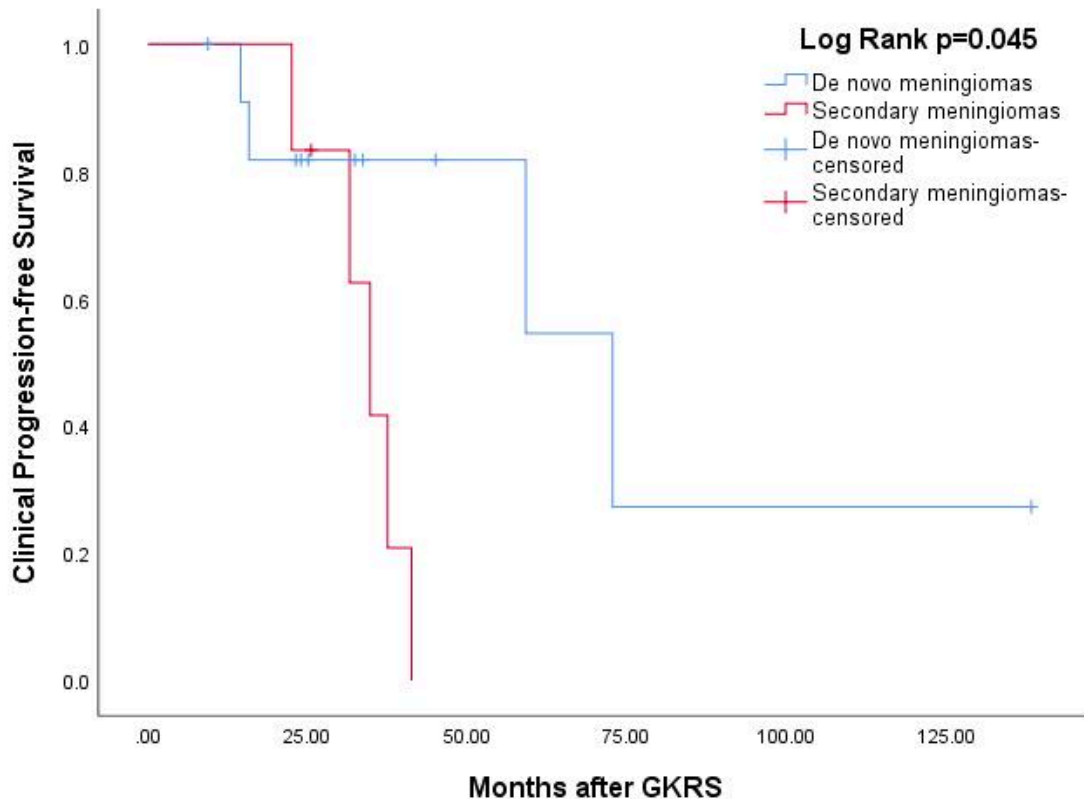


Figure 4

Kaplan-Meier curve of clinical PFS of secondary VS de novo grade 2 meningiomas ($p=0.045$).

