Grade II meningiomas and Gamma Knife radiosurgery: analysis of success and failure to improve treatment paradigm

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OBJECTIVE Grade II meningiomas, which currently account for 25% of all meningiomas, are subject to multiple recurrences throughout the course of the disease and represent a challenge for the neurosurgeon. Radiosurgery is increasingly performed for the treatment of Grade II meningiomas and is quite efficient in controlling relapses locally at the site of the lesion, but it cannot prevent margin relapses. The aim of this retrospective study was to analyze the technical parameters involved in producing marginal relapses and to optimize loco-marginal control to improve therapeutic strategy.

METHODS Eighteen patients presenting 58 lesions were treated by Gamma Knife radiosurgery (GKRS) between 2010 and 2015 in Hôpital de la Pitié-Salpêtrière. The median patient age was 68 years (25%–75% interval: 61–72 years), and the sex ratio (M/F) was 13:5. The median delay between surgery and first GKRS was 3 years. Patients were classified as having Grade II meningioma using World Health Organization (WHO) 2007 criteria. The tumor growth rate was computed by comparing 2 volumetric measurements before treatment. After GKRS, iterative MRI, performed every 6 months, detected a relapse if tumor volume increased by more than 20%. Patterns of relapse were defined as being local, marginal, or distal. Survival curves were estimated using the Kaplan-Meier method, and the relationship between criterion and potential risk factors was tested by the log-rank test and univariable Cox model.

RESULTS The median follow-up was 36 months (range 8–57 months). During this period, 3 patients presented with a local relapse, 5 patients with a marginal relapse, and 7 patients with a distal relapse. Crude local control was 84.5%. The local control actuarial rate was 89% at 1 year and 71% at 3 years. The marginal control actuarial rate was 81% at 1 year and 74% at 2 years. The distal control actuarial rate was 100% at 1 year, 81% at 2 years, and 53% at 3 years. Median distal control was 38 months. Progression-free survival (PFS) was 71% at 1 year, 36% at 2 years, and 23% at 3 years. Median PFS was 18 months. Lesions treated with a minimum radiation dose of ≤ 12 Gy had significantly more local relapses than those treated with a dose > 12 Gy ($p = 0.04$) in univariate analysis.

Marginal control was significantly influenced by tumor growth rate, with a lower growth rate being highly associated with improved marginal control ($p = 0.002$). There was a trend toward a relationship between dose and marginal control, but it was not significant ($p = 0.09$). PFS was significantly associated with delay between first surgery and GKRS ($p = 0.03$). The authors noticed few complications with no sequelae.

CONCLUSIONS In order to optimize loco-marginal control, radiosurgical treatment should require a minimum dose of > 12 Gy and an extended target volume along the dural insertion. Ideally, these parameters should correspond to the aggressiveness of the lesion, based on genetic features of the tumor.

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KEY WORDS stereotactic radiosurgery; atypical; grade II meningioma; marginal relapse; Simpson grade

ABBREVIATIONS 3D-SPGR = 3D-spoiled gradient recalled; FRT = fractionated radiation therapy; GKRS = Gamma Knife radiosurgery; PFS = progression-free survival; SRS = stereotactic radiosurgery; TGR = tumor growth rate; WHO = World Health Organization.

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RECENT modifications to the World Health Organization (WHO) 2007 and 2016 criteria defining Grade II meningioma have dramatically increased its frequency. Grade II meningioma currently accounts for about 25% of all meningiomas, which are the most frequent intracranial primary tumors in adults.^{17,22}

Since the beginning of neurosurgery with Harvey Cushing, these tumors have represented a challenge for the neurosurgeon. Although they can be easily resected once or even several times with apparent total resection, they often recur at the original lesion site or at a distal location within the CNS.^{6,20,24} Previously, when tumor residue was left in place because of close or invaded critical structures (i.e., venous sinuses, cavernous sinus, cranial nerves), serial MRI was performed to detect potential progression, and when required, a second surgery or a conformal irradiation was planned. This came with the risk of possible side effects for the patient, such as edema, radionecrosis, or cognitive impairment.^{12,16}

The emergence of Gamma Knife radiosurgery (GKRS) as an efficient and well-tolerated therapeutic alternative has transformed this paradigm, since treatment can be applied in various situations, namely as an adjuvant treatment, a treatment for relapses without prior irradiation, or a salvage treatment.^{10,11,13,25}

Nevertheless, despite the local efficacy of GKRS, relapses are frequent and can progressively lead to a loss of control of the disease. These relapses may be local, marginal, or distal in nature.^{4,19} While distal relapses are part of the natural history of the disease, local and marginal failures might be related to technical issues, such as choice of dose and target.^{5,23}

Although patterns of relapse have been described in several studies, few have focused on the parameters specific to marginal relapses.⁵

The ability of meningiomas to become more aggressive during the course of the disease has already been established.^{15,18} Better knowledge about the behavior of these tumors, including their growth patterns and growth rate, should help clinicians to more accurately assess their malignancy and, therefore, to better design an optimized dosimetric plan.

Thus, the aims of this study were twofold: 1) to describe tumor growth patterns and growth rates in this cohort of patients, and 2) to analyze parameters contributing to loss of local and marginal control, in order to optimize treatment plans.

Methods

Patients

Eighteen patients with 58 lesions were treated at Hôpital de la Pitié-Salpêtrière for Grade II meningioma between 2010 and 2015. The median patient age was 68 years (25%–75% interval: 61–72 years). The sex ratio (M/F) was 13:5. Six patients had 1 previous craniotomy, 8 had 2 procedures, and 4 had 3 procedures (Table 1). The median delay between surgery and GKRS was 3 years. No patients had a history of chemotherapy. All 18 patients underwent GKRS at the time of recurrence after prior surgery. Four of these 18 patients were classified as receiving salvage GKRS because they had already received

TABLE 1. Patient demographics

Variable	Value
No. of patients	18
Median age in yrs (25%–75% interval)	68 (61–72)
Sex (M/F)	13:5
Median time in yrs btwn op & 1st radiosurgery (25%–75% interval)	3 (1.46–4.97)
No. of patients w/ previous irradiation (%)	6 (33.3)
No. of patients w/ systemic antitumoral treatment (%)	0 (0)
No. of surgeries per patient	
1 surgery	6
2 surgeries	8
3 surgeries	4

radiation on the target volume: 2 patients had undergone external-beam radiation therapy after the first surgery, and 1 patient had been given whole-brain radiation therapy for a hematological malignancy 10 years before surgery. The last patient was treated with stereotactic radiotherapy sessions after surgery. In addition, 2 patients previously received irradiation distant from the site of GKRS. Twelve patients underwent GKRS for the treatment of recurrent disease without previous irradiation. No patient received adjuvant GKRS.

Lesions Characteristics

Altogether, 58 lesions were treated in our cohort of 18 patients: 24 lesions were treated during a first session of GKRS in 18 patients, 23 lesions during a second session in 15 patients, and 6 lesions during a third session in 4 patients. In 1 patient, 4 lesions were treated during a fourth session, and 1 lesion was treated in a fifth session.

The lesions were located in the falx cerebri ($n = 30$), convexity ($n = 20$), tentorium cerebelli ($n = 3$), and skull base ($n = 5$; Table 2). The median lesion volume was 2.5 cm³ (range 0.1–14 cm³).

The lesions were classified as postoperative residues in 8 cases, lesions at the craniotomy site (surgical bed and dura mater) in 27 cases, lesions distant from the craniotomy site in 17 cases, and relapses after GKRS in 6 cases.

Tumor growth rate (TGR) before GKRS was computed by comparing 2 volumetric measurements (initial MRI and MRI on the day of GKRS) during the interval between these exams: $TGR = (V_{RS} - V_i) / (t_{RS} - t_i)$ (V = volume; t = time; RS = radiosurgery; i = initial). The median TGR was 3.5 cm³/year. TGR varied widely among lesions, ranging from 0.1 to 45 cm³/year.

GKRS

A Leksell head frame was applied to the patient's head under local anesthesia, and 3D-spoiled gradient recalled (3D-SPGR) gadolinium-enhanced MRI and 1-mm thick CT scans were obtained. These images were codefined on GammaPlan software. Dosimetry was realized according to tumor volume, with a prescription dose of 14–16 Gy at 50% isodose.

Treatment plans were approved by a team consisting

TABLE 2. Lesion characteristics

Variable	Value
No. of lesions	58
Nature of lesions	
Postop residue	8
Recurrence at craniotomy site	27
Recurrence outside craniotomy site	17
Marginal relapse of previous radiosurgery	5
Local relapse of previous radiosurgery	1
Tumor location	
Falx cerebri	30
Convexity	20
Tentorium cerebelli	3
Skull base	5
Tumor vol in cm ³ (range)	2.5 (0.1–14)
Dosimetry	
Median min dose in Gy (0–100 interval)	15 (8–19)
Median max dose in Gy (0–100 interval)	32 (24–40)

of a neurosurgeon, a radiation oncologist, and a medical physicist.

Pathology and Grading

All patients were classified as having Grade II meningioma according to 2007 WHO criteria.

Imaging and Volumetry

After the first GKRS treatment, iterative MRI was performed every 4–6 months to detect a relapse or a response of the treated lesion. A 3D contrast-enhanced, T1-weighted sequence was performed with 1.2-mm-thick isotropic slices. Each slice was delineated by a resident (M.F.) and a senior neurosurgeon (C.A.V.). Volumetry was assessed by GammaPlan software.

A growing lesion was defined as a relapse if the tumor volume increased by more than 20% when compared with its measurement on the day of treatment.¹⁸ Otherwise, the lesion was defined as controlled.

Assessment of Relapse Patterns

As described elsewhere,^{9,18,25} a relapse occurring inside the field of treatment (“in-field”) was called a local relapse; when it occurred at the border of a previously treated lesion, it was considered to be a marginal relapse. Each treated lesion was assessed for local and marginal control, taking into account the delay between GKRS and last MRI.

A distal relapse was defined as a relapse occurring in a remote location outside the first treatment area. The first relapse was the only one taken into account. Out-of-field relapse (i.e., marginal plus distal relapse), distal relapse, and progression-free survival (PFS) were calculated for the patient and not by lesion.

Statistical Analysis

Study criteria included time to local relapse, time to distal relapse, time to marginal relapse, time to outfield

relapse, and PFS. Each criterion was analyzed for survival analysis. Survival curves were calculated by the Kaplan-Meier method, and the relationship between each criterion and potential risk factor was tested by the log-rank test for qualitative variables and by the univariable Cox model for quantitative variables. The potential risk factors analyzed in this study were patient age, sex, tumor volume, minimum and maximum dose, previous radiotherapy, delay between surgery and GKRS, and tumor topography. Statistical computations were performed using the SAS V9.3 statistical package (SAS Institute Inc.).

Results

Patterns of Relapse and Retreatment

The median follow-up period was 36 months (range 8–57 months). Crude local control was 84.5%.

During this time period, 3 patients presented with a local relapse, 5 with a marginal relapse, and 7 with a distal relapse (Fig. 1). Therefore, at the time of our analysis, 83.3% of patients had a relapse.

Among the patients in whom a recurrent lesion developed, 14 had a second GKRS; among them, 6 had a local relapse or a marginal relapse. In addition, 2 underwent both a surgery and fractionated radiation therapy (FRT); 1 underwent FRT and 1 was treated with chemotherapy. Of patients who underwent reoperation, 1 had a tumor that showed progression from Grade II toward Grade III.

Survival Curves

Survival curves were calculated to illustrate the time to local relapse, time to marginal relapse, time to distal relapse, time to outfield relapse, and PFS (local + marginal + distal; Fig. 2). The local control actuarial rate was 89% at 1 year and 71% at 3 years. The marginal control actuarial rate was 81% at 1 year and 74% at 2 years. The distal control actuarial rate was 100% at 1 year, 81% at 2 years, and 53% at 3 years. Median distal control was 38 months. The out-of-field control actuarial rate was 92% at 1 year, 68% at 2 years, and 42% at 3 years. Median out-of-field control was 33 months.

Finally, PFS was 71% at 1 year, 36% at 2 years, and 23% at 3 years. The median PFS was 18 months.

Univariate Analysis

Among parameters tested in a univariate analysis, lesions treated with a minimum dose of ≤ 12 Gy had significantly more local relapses than those treated with a dose of > 12 Gy ($p = 0.04$; Fig. 3). However, TGR and tumor volume were not significantly associated with local control.

Marginal control was significantly influenced by TGR, with a lower TGR being highly correlated with improved marginal control ($p = 0.002$). There was a trend toward a relationship between dose and marginal control, but it was not significant because of a lack of power ($p = 0.09$).

In addition, PFS was significantly associated with a delay between first surgery and GKRS ($p = 0.03$).

Complications

Among this group of patients, we observed 2 patients

FIG. 1. Patterns of relapse. **A:** Marginal relapses at the border of a previously irradiated lesion (red arrows). **B:** Local relapse (red arrows), completely surrounding the previously treated lesion. **C:** Distal relapses (red arrows), far from the first treated lesion.

with radionecrosis, which was treated by corticosteroids; no surgery was required. There was also a patient who presented with a spontaneous hemorrhage and another with recurrent seizures. No long-term consequences were noticed.

Discussion

Meningiomas are typically benign lesions, but their ability to recur even decades after a good resection is well known.²⁴ Grade II meningiomas have been recently redefined by new classification criteria that account for brain invasion as well as the usual histological features. With these new criteria, the incidence of Grade II tumors, which recur earlier and in a more diffuse manner than benign meningiomas, grows from 3%–4% to 20%–30%.¹⁷ Moreover, Grade II meningiomas are very heterogeneous and thus difficult to analyze in terms of PFS. Indeed, some display no mitoses and only brain invasion, while others are very aggressive histologically, with up to 19 mitoses/10 hpf (20 mitoses or more is a defining characteristic of Grade III meningiomas).

Relapse Patterns

The pattern of relapse for Grade II meningiomas is wide, and this heterogeneity is not well understood. Some tumors will only recur locally, while others will recur in a distal location. However, marginal relapses at the border of a previously treated lesion are a common occurrence for this group of tumors.^{1,4,5,10,19} Focused treatments, such as surgery and GKRS, can temporarily control new le-

sions, but their high incidence and tendency to invade and progress along the dural structures will eventually prohibit long-term control of the disease.² Some authors choose to study relapses according to surgical bed, whereas others focus on the pattern of relapses according to the radiosurgical field. We chose the latter approach.^{9,19,26}

Marginal lesions have been inconsistently described in the literature. A majority of authors pool together marginal and distal failures.^{1,3,5,26} Others define marginal failures as recurrent lesions occurring at the contact of a previously treated lesion^{18,19} or at a distance less than 2 cm from a previously treated tumor.⁹ In our study, we defined marginal failures as new nodules growing at the border of a previously treated lesion and found their occurrence to be associated with TGR.

It is commonly acknowledged that an efficient resection of a meningioma, even when benign, is one that requires removal of more tissue than the tumor itself.²⁴ The resection must incorporate part of the dura mater surrounding the insertion to avoid early relapses.

Resection of cerebral parenchyma invaded by Grade II meningioma has not been evaluated in terms of recurrence. The occurrence of marginal relapses is possible evidence of some remaining tumor at the vicinity of its insertion that was not controlled by the radiosurgical prescription isodose. Following this idea, lack of local control might be related to the choice of dose, and marginal relapse might be due to inappropriate targeting. Therefore, improvements in both issues should require an optimized dose at reference isodose and a larger target than commonly used,²³ i.e., a margin surrounding contrast enhancement.^{5,21}

FIG. 2. Kaplan-Meier curves showing time without local relapse (A), time without marginal relapse (B), survival with no distal relapse (C), and PFS (D).

FIG. 3. Local control according to minimal dose. Kaplan-Meier curve showing a cutoff at 12 Gy for the minimal dose. A dose higher than 12 Gy was associated with improved local control ($p = 0.04$).

TABLE 3. Comparison of major SRS series reporting on Grade II meningiomas

Authors & Year	WHO Grade	No. of Patients w/ WHO II Lesions	Median Tumor Vol (cm ³)	Median Tumor Margin Dose (Gy)	Local Control*	Regional Control	Statistical Analysis			
							PFS	OS	Local	Regional
Pollock et al., 2012	II III	37 (50 total)	14.6	15	85% 1 yr, 45% 5 yrs	NA	76% 1 yr, 40% 5 yrs	90% 1 yr,† 62% 5 yrs† (Grade II, 97% 1 yr, 80% 5 yrs)	>14.6 cm ³ , FPRT WHO grade	NA
Attia et al., 2012	II	24	NA	14	75% 1 yr, 51% 2 yrs, 44% 5 yrs	NA	40% 2 yrs, 25% 5 yrs	92% 1 yr, 67% 2 yrs, 52% 5 yrs	Conformity index	NA
Hanakita et al., 2013	II	22 (28 lesions, 39 sessions)	6	18	74% 1 yr, 39% 2 yrs, 16% 5 yrs	NA	NA	91% 1 yr, 68% 2 yrs, 68% 5 yrs	>6 cm ³ , <18 Gy, KPS <90	NA
Bultuis et al., 2014	II	34	3.5	11–15‡	83% 2 yrs, 64% 5 yrs	No out-of-field progression	NA	NA	Sex, WHO grade	NA
Aboukais et al., 2015	II	27 (34 sessions)	5.4§	15.2§	75% 1 yr, 52% 2 yrs, 40% 3 yrs	75% 1 yr, 48% 2 yrs 33% 3 yrs	NA	NA	Age, vol	Sex, no. of surgeries, SRS setting
Wang et al., 2016¶	II III	37 (+ 9 Grade III)	11.7	12.5	91% 1 yr, 59% 2 yrs, 39% 3 yrs	NA	83% 1 yr,§ 30% 2 yrs, 20% 5 yrs	97% 3 yrs, 88% 5 yrs	Sex, <13 Gy	NA
Kaprealian et al., 2016**	I II III No	48 (264 patients, 406 lesions)	NA	NA	56% 5 yrs, Grade II only	NA	NA	NA	Sex, WHO grade, SRS setting	NA
Our study	II	18	2.5	15	89% 1 yr, 71% 3 yrs	92% 1 yr, 68% 2 yrs, 42% 3 yrs	71% 1 yr, 36% 2 yrs, 23% 3 yrs	100% 1 yr, 55% 3 yrs	>12 Gy, vol, GR	GR, dose
										ISRS
										NA

FPRT = failure of previous radiotherapy; GR = growth rate; ISRS = interval between surgery and radiosurgery; KPS = Karnofsky Performance Scale; NA = not available; No = not operated; OS = overall survival.

* Local control includes in-field relapse (marginal relapse not included), except in the study by Attia et al., where local relapse and relapse occurring within < 2 cm are pooled.

† In study by Pollock, death is analyzed as meningioma-related death, with no distinction between Grade II and Grade III.

‡ In study by Bultuis, median minimal dose.

§ In study by Aboukais, mean dose and mean target volume.

¶ In study by Wang, separate analysis was performed for Grade II and Grade III meningiomas; results for Grade II are shown in this table, except for tumor volume and margin dose where Grade II and Grade III are pooled.

** In study by Kaprealian, Grades I, II, and III are pooled except for local freedom from progression, which is analyzed separately for each grade.

In our study, we considered marginal failures apart from distal relapses. In fact, marginal and local control should be grouped together for matters related to efficacy. Our results show that under a minimum delivered dose of 12 Gy, the probability of local control is low. The local control rate and PFS were comparable to those previously published,^{4,19,26} but the median volume treated in our study was the lowest in the literature (Table 3). Among papers studying the relationship between minimum dose and local control, Wang et al. found a cutoff at 13 Gy, and Attia et al. reported a cutoff at 15 Gy.^{4,26} Sethi et al. reported that the prescription dose should not be lower than 16 Gy.²³

Risk of Malignant Progression

The ability of Grade II tumors to progress to Grade III during the course of their evolution is well established and is typically due to the accumulation of genetic events such as TERT promoter mutations and loss of *CDKN2AB* expression.^{7,8} One unresolved issue concerns tumor grading at relapse. At the time of recurrence, it is unclear and unverifiable as to whether meningiomas are still Grade II or if they have transformed to Grade III. This possibility could explain the rapid growth (acceleration of growth) of some meningiomas at a distance from the site of GKRS or surgery. One approach for estimating malignancy could be to measure their growth rate before treatment.¹ We analyzed this parameter in our study and found it to be significantly associated with risk of marginal relapse.

The risk of relapse could be more accurately predicted by analysis of specific gene alterations on the initial tumor that are used as biomarkers to identify meningiomas at risk for malignant transformation. Therefore, dosimetry could be tailored to fit with the potential malignancy of the tumor.

In addition, the significant number of relapses occurring at the site of craniotomy might justify performing a systematic irradiation of the surgical cavity bed after resection by GKRS or, if required, by stereotactic radiotherapy. In all cases, a close follow-up and the use of iterative procedures including surgery and GKRS are of great importance.

Study limitations include the following: 1) the low number of patients that may influence results of statistical correlations because of lack of power, 2) the potential for histological progression at the time of the relapse that may result in treating Grade III meningiomas rather than Grade II, and 3) our focus on individual target lesions rather than total tumor burden, which may affect our interpretation of data and not represent the global status of the disease.

Conclusions

In this study, we described patterns of relapse and tried to accurately analyze factors involved in local and marginal control of Grade II meningioma after GKRS. We found that a 12-Gy minimum radiation dose and TGR to be significantly associated with local and marginal control, respectively. Thus, an optimized radiosurgical treatment plan should require appropriate doses delivered to the lesion and larger target volumes, including dural insertion. Ideally, these parameters should correlate with the true aggressiveness of the lesion, based on genetic features of the

tumor. A close follow-up and the use of various therapeutic approaches, including surgery, targeted therapies, and focused irradiation are of utmost importance.

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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: Valery, Kalamarides. Acquisition of data: Valery, Faillot, Lamproglou, Jenny. Analysis and interpretation of data: Valery, Faillot, Mokhtari, Kalamarides. Drafting the article: Valery. Critically revising the article: Valery, Peyre, Mazon, Cornu, Kalamarides. Reviewed submitted version of manuscript: Valery, Kalamarides. Approved the final version of the manuscript on behalf of all authors: Valery. Statistical analysis: Lamproglou, Golmard. Study supervision: Valery.

Supplemental Information

Previous Presentations

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