Journal of Neuro-Oncology (2020) 147:441–450
https://doi.org/10.1007/s11060-020-03440-9

CLINICAL STUDY

Long-term outcomes of multimodality management for parasagittal meningiomas

Lingyang Hua[1] · Daijun Wang[1] · Hongda Zhu[1] · Jiaojiao Deng[1] · Shihai Luan[1] · Haixia Chen[2] · Shuchen Sun[1] · Hailiang Tang[1] · Qing Xie[1] · Hiroaki Wakimoto[3] · Ye Gong[1,4]

Received: 19 October 2019 / Accepted: 17 February 2020 / Published online: 22 February 2020

Abstract

Purpose The aim of this study was to systematically analyze the clinical characteristics of a large cohort of parasagittal meningioma (PM) and to evaluate the patients' outcomes and best treatment strategies based on tumor features.

Methods To minimize selection bias we performed a single-institutional review of PM with restricted criteria. One hundred and ninety-two consecutive patients who met criteria for inclusion were reviewed from 2003 to 2011 in our general hospital.

Results A total of 131 cases (68.2%) were with WHO grade I, while grade II and grade III PMs constituted 40 (20.8%) and 21 cases (10.9%). Higher histological grade was associated with loss of trimethylation of H3K27 (P = 0.000). For WHO grade I PMs, GTR was significantly associated with a better PFS (P = 0.023); however, adjuvant radiotherapy did not benefit patients with STR (P = 0.215). For de novo high-grade (WHO grade II and III) PMs (n = 37), adjuvant radiotherapy was associated with a significantly longer OS (P = 0.013), while no difference was observed between GTR and STR (P = 0.654). In recurrent high-grade PM patients (n = 24), GTR combined with adjuvant radiotherapy increased PFS (P = 0.005).

Conclusions This study demonstrated that PMs were a heterogeneous group of tumors with a high proportion of high-grade tumors that often displayed aggressive clinical behaviors. Low-grade PM benefited from radical resection, whereas high-grade de novo PM did not. Adjuvant radiotherapy significantly prolonged OS for high-grade primary PM, but did not impact survival of patients with subtotally resected low-grade tumors. Long-term outcome of high-grade recurrent PMs was dismal. We thus show that extent of tumor resection, tumor grade and tumor recurrent status inform therapeutic decisions for PMs.

Keywords Parasagittal meningioma · Radiation · Overall survival · Prognosis · Recurrence · H3K27Me3

Lingyang Hua and Daijun Wang are co-first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11060-020-03440-9) contains supplementary material, which is available to authorized users.

✉ Hiroaki Wakimoto
hwakimoto@mgh.harvard.edu

✉ Ye Gong
drgongye@163.com

[1] Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, 12# Middle Wulumuqi Road, Jingan District, Shanghai 200040, China

[2] Department of Neuropathology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

[3] Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[4] Department of Critical Care Medicine, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

Abbreviations

PM	Parasagittal meningioma
PFS	Progression free survival
OS	Overall survival
CNS	Central nervous system
WHO	World Health Organization
KPS	Karnofsky performance score
GTR	Gross total resection
STR	Subtotal resection

Introduction

Parasagittal region is one of the most common locations of meningioma growth, accounting for 18–23% of all intracranial meningiomas [1–3]. As suggested by its name, parasagittal meningiomas (PMs) are those that fill the parasagittal angle, and without any brain tissue between the superior sagittal sinus and the tumor. Its essential association with

the superior sagittal sinus and drainage veins makes it difficult to achieve radical resection which may lead to lasting neurological deficits, especially when the tumor is located at the middle 1/3 and with superior sagittal sinus invasion. Treatment strategies for this special subtype tumor remain controversial, especially when regarding the extent of resection (EOR) and post-operative radiation therapy. Some neurosurgeons hold that, whenever possible, an initial attempt of Simpson Grade I resection should be achieved, which can significantly prolong patients' progression free survival (PFS). While others argue that since most tumors are benign in nature, with a WHO Grade I, patients can benefit more with a subtotal resection combined with a close follow-up [4–9]. The number of studies specifically investgeting parasagittal meningioma has been relatively small [10–13]. Most patient series reported previously are either with small patient numbers or short-term follow-up. Here we conducted a systematic analysis of the epidemiology, clinical features and long-term prognostic factors of PM treated and followed long-term at the east branch of our neurosurgical center with the goal to inform an optimal treatment strategy. To the best of our knowkedge, this cohort of patients with PM is the largest in scale to date, with long follow-up periods averaging over 8 years.

Patients and methods

Patients population

A total of 192 patients with surgically treated PM were enrolled in our study. The inclusion criteria were: (1) Patients who received surgical resection of PM at the east campus of Huashan Hospital with intact clinical information. (2) Pathologically diagnosed as meningioma according to the newest WHO 2016 meninioma grading criterion. (3) Pre and postoperative T1WI enhanced MR images were available. (4) Follow-up data were available. Detailed clinical information and follow-up data including age, gender, presenting symptoms, neurological functions, duration of symptoms, invasion of the sinus, tumor location, EOR were extracted from medical records for final analysis. The sagittal location was classified as anterior, middle and posterior 1/3, which was determined by the location of the main tumor body according to sagittal preoperative MR images. The EOR was evaluated based on surgical records according to the Simpson grading scale and confirmed with post-operative enhanced T1WI MRI reviewed by an experienced neuroradiologist (Dr. Hanqiu Liu) who was blinded to patients' general information. Simpson Grade I–II resection was defined as gross total resection (GTR), while grade III–V resection was defined as sub-total resection (STR). Extent of tumor invasion to the sinus was evaluated according to the Sindou and Alvernia Classification [5]. Sindou and Alvernia Grade I was defined as minor sinus invasion, grade II–IV defined as middle sinus invasion, while grade V–VI regarded as major sinus invasion. Bone invasion was also recorded according to the surgical and pathological records.

Patient consent was not required since our study did not include any usage of personal information or collection of patient samples other than medical need. The study was approved by the Human Subjects Institutional Review Board at our hospital.

Immunohistochemistry

Immunohistochemistry was performed on 4-μm-thick formalin-fxed, parafn-embedded (FFPE) tissue sections. EMA, Vimentin and PR were used as a routine diagnostic marker after surgeries, and H3K27me3 staining was performed for research purpose. Detailed protocol of H3K27me3 staining was described previously [14]. Positive staining in less than 50% of cells was considered negative.

Statistics

All analyses were performed with Stata 13.3 software (StataCorp, College Station, TX). Continuous clinical features were summarized with descriptive analysis and analyzed with Student *t* test or Mann–Whitney U test, while categorical variables were analyzed with either Pearson chi-square test or Fisher's exact test. Log-rank test was applied for survival analysis. Covariates with a univariable $P < 0.05$ were included in the multivariable logistic regression model to determine factors that were independent for PFS and overall survival (OS) outcomes. Clinical factors considered for prognostic and functional outcome analysis included: age (< 60 years vs ≥ 60 years), gender (female vs male), WHO grade (low grade vs high grade), symptom duration (< 8 months vs ≥ 8 months), treatment status (de novo vs recurrent), preoperative neurological function (KPS < 80 vs KPS ≥ 80), Simpson resection grade (GTR vs STR), Ki-67 index (< 3 vs ≥ 3), tumor sagittal location (anterior 1/3 vs middle 1/3 vs posterior 1/3) and histone H3K27 trimethylation (H3K27me3) (positive vs negative). *P* values less than 0.05 were considered statistically significant.

Results

Patients characteristics

A total of 192 PM cases (110 females and 82 males) with detailed clinical information, radiological images and prognostic data were enrolled for the final analysis. Among them, 131 cases were WHO grade I (68.2%), 40 cases were

grade II (20.8%), and 21 cases were grade III (10.9%). The detailed pathological subtype distribution was listed in Table 1. The mean age at diagnosis was 51.9 ± 11.5 years old (range, 18–80 years). The mean symptom duration was 17.3 ± 37.0 months (range, 0.25–240 months). The median KPS score at diagnosis was 80 (range, 40–100). Symptoms at onset were largely related to the proximity of the tumor to the rolandic fissure. Nearly one-fourth of patients reported seizure (43, 22.4%) at presentation, followed by headache (38, 19.8%), hemiparesis (28, 14.6%), vertigo (23, 12.0%), monoparesis (26, 13.5%), cognitive decline (3, 1.6%), calvarial deformity (5, 2.6%), visual symptoms (5, 2.6%) and speech disturbance (3, 1.6%). The remaining 18 patients (9.4%) did not present with any symptoms at onset; their tumors were incidentally found by MRI. A lower preoperative KPS score (P = 0.008) and recurrent status (P = 0.003) was associated with preoperative seizures. No other factors including age (P = 0.255), gender (P = 0.074), histological grade (P = 0.373), H3K27me3 staining (P = 0.428), Ki-67 index (P = 0.452), bone invasion (P = 0.557), or sagittal location (P = 0.78) was correlated with seziures.

A total of 87 PMs (45.3%) were located at the anterior third of the superior sagittal sinus (SSS), 76 (39.6%) at the middle third and 29 (15.1%) at the posterior third. The most common presenting symptom for anterior, middle and posterior third PMs were focal or generalized seizure (25.3%, 22/87), contralateral paralysis (32.9%, 25/76), and headache (37.9%, 11/29), respectively.

Recurrent and malignant transformation

In our cohort, 32 patients (16.7%) were diagnosed with recurrent PM, who received at least one surgical procedure before at local hospitals or our neurosurgical center. Among them, one patient with frontal PM received five tumor resections before, two patients had three previous surgical

Table 1 Clinical characteristics of 192 patients with parasagittal meningioma

Characteristics	Value	Characteristics	Value
Age, years	51.94 ± 11.55 (range, 18–80)	New sinus invasion grade	
Gender		Minus invasion	57 (29.7%)
Male	82 (42.7%)	Moderate invasion	84 (43.8%)
Female	110 (57.3%)	Severe invasion	51 (26.6%)
Presenting symptoms		WHO grade	
Seizure	43 (22.4%)	Grade I	131 (68.2%)
Headache	38 (19.8%)	Fibrous	97 (50.5%)
Hemiparesis	28 (14.6%)	Meningethalial	21 (10.9%)
Monoparesis	26 (13.5%)	Angiomatous	6 (3.1%)
Vertigo	23 (12.0%)	Psammomatous	3 (1.6%)
No symptoms	18 (9.4%)	Translational	2 (1.0%)
Calvarial deformity	5 (2.6%)	Lymphoplasmacyte	1 (0.5%)
Visual symptoms	5 (2.6%)	Microcystic	1 (0.5%)
Cognitive decline	3 (1.6%)	Grade II	40 (20.8%)
Speech disturbance	3 (1.6%)	Atypical	39 (20.3%)
Location		Chordoid	1 (0.5%)
Anterior 1/3	87 (45.3%)	Grade III	21 (10.9%)
Middle 1/3	76 (39.6%)	Anaplastic	19 (9.9%)
Posterior 1/3	29 (15.1%)	Papillary	2 (1%)
		Recurrent status	
Pre-operative KPS	90 (range 40–100)	Primary	160 (83.3%)
Sindou&Alvernia Classification		Recurrent	32 (16.7%)
I	57 (29.7%)	Malignant transformation	14 (7.3%)
II	29 (15.1%)	H3k27me3 methylation loss	32 (16.7%)
III	39 (20.3%)	In grade I	6 (4.6%)
IV	16 (8.3%)	In grade II	7 (17.5%)
V	9 (4.7%)	In grade III	19 (90.5%)
VI	42 (21.9%)	Median Ki-67 index, %	2 (range, 1–15)
Symptom duration	17.3 ± 37.0 (range, 0.25–240)	Follow-up, months	101.9 ± 33.8 (range, 4–209)

WHO World Health Organization, *KPS* Karnofsky performance score, *GTR* gross total resection

resections, seven patients had two previous surgical resections and the remaining 23 patients received one previous surgical resection.

Malignant transformation was defined as previously described [15]. Of 32 recurrent meningiomas, 14 (43.8%) of them had a history of lower grade meningioma surgery and were regarded as malignant transformation. Among them, 9 were anaplastic and 5 atypical. All the 5 atypical cases progressed from fibrous meningioma. For the 9 anaplastic PMs, 5 progressed from atypical subtypes, and 3 from meningothelial. One anaplastic meningioma was second recurrence and was initially diagnosed with fibrous meningioma and later atypical at the first recurrence.

Pathology and Immunohistochemistry of H3K27me3

The detailed distribution of histopathological subtypes in our cohort was listed in Table 1. Fibrous was the most common grade I subtype, atypical for grade II and anaplastic for grade III.

A total of 32 PMs (16.7%) showed H3K27me3 negative staining, and it was 4.6% (6/131) in grade I, 17.5% (7/40) in grade II and 90.5% (19/21) in grade III tumors (Supplemental Fig. 1). Higher histological grade was associated with loss of trimethylation of H3K27 (P = 0.000, Fisher's exact test). Further analysis revealed that recurrent PMs also showed significantly higher frequency of H3K27me3 loss (P = 0.001, Fisher's exact test), with 12.5% (20/160) and 37.5% (12/32) of primary and recurrent cases, respectively. A detail analysis into the subsets of recurrent PMs showed that, tumors with malignant transformation harbored H3K27me3 loss more frequently than non-malignant transformation tumors (P = 0.001, Fisher's exact test). However, no association between H3K27me3 and SSS invasion status was detected (P = 0.405).

Radiotherapy

In general, adjuvant radiation was recommended to both atypical and anaplastic meningioma patients, regardless of GTR or STR. Recently, however, with a deeper understanding of history of these subsets of meningiomas, radiation has not been recommended for grade II tumors with GTR [16]. Potential benefits and adverse events of radiation therapy were discussed with the patients and families, who then made the final decision. A total of 42 patients in our series received postoperative radiotherapy in different forms 2 to 4 weeks after the initial surgery. Among them, 34 patients received traditional external beam radiotherapy in 2 daily fractions with 1–2 cm clinical target volume and 3–5 mm planning target volume (mean dose 40.8 ± 8.5 Gy, range 30–66 Gy). Five patients received Gamma Knife surgery for the remaining tumors with a prescription dose of 14.0 Gy at the 50% isodose line (28.0 Gy at the 100% isodose line). Another 3 patients received CyberKnife with 44 Gy in 5 fractions. No patients in our series received any form of chemotherapy.

We compared the baseline characteristics including age, gender, EOR, and tumor recurrent status between the radiated group and the no-radiated group, and found that there was no difference between age (P = 0.08) and EOR (P = 0.099). However, recurrent patients (P = 0.021) were more likely to receive postoperative radiation, which was consistent with our previous knowledge that recurrent status was associated with a worse outcome, so a more aggressive treatment strategy was usually recommended for these patients. In addition, there was a difference of gender distribution (P = 0.000) between the radiated and non-radiated group. Male patients were predominant in the radiated group.

Surgical procedure

Simpson Grade I resection was achieved in 100 patients (52.1%), grade II in 65 patients (33.9%), grade III in 7 patients (3.6%), and grade IV in the remaining 20 patients (10.4%). Fifty-seven patients (29.7%) were classified as Sindou and Alvemia grade I, 29 patients (15.1%) as grade II, 39 patients (20.3%) as grade III, 16 cases (8.3%) as grade IV, 9 cases (4.7%) as grade V and the rest 42 cases (21.9%) as grade VI. We further reclassified Sindou and Alvemia grade into three grades based on our experience of handling the SSS during the surgery. Sindou and Alvemia Grade I was regarded as minimal invasion, grade II to IV as moderate invasion, while grade V–VI as severe invasion. GTR was achieved in all 57 patients with minimal invasion tumors (100%) and in 94.1% patients (48/53) with severe invasion tumors, while for moderate invasion tumors, GTR was achieved in 71.4% patients (60/84). Interestingly, radical resections were more likely to be achieved for minor (P = 0.003, Fisher's exact test) and severe sinus invasion tumors (P = 0.000, Fisher's exact test) than for moderate invasion tumors. However, no association was observed between the EOR and PM histological grade (P = 0.161, Fisher's exact test). Bone invasion was observed in 28 cases (14.6%), and for these patients, affected skull was removed for decompression purpose in 39.3% (11/28) and for the rest 60.7% skull (17/28) was returned after abrasion of the inner plate of calvaria.

Thirteen patients experienced some kind of post-operative complications (6.8%). Eleven of them had a post-operative intracranial hematoma within 48 h after surgery, and 8 patients received a hematoma removal surgery. Two other patients presented seizure attack within 24 h after surgery. Among these 13 patients, 7 received GTR and 6 received

STR, so post-operative complication rate was 4.2% in GTR surgeries and 22.2% in STR surgeries (P = 0.004, Fisher's exact test). No patient died within 30 days after surgery.

Outcome and survival analysis

The patients in our series were followed-up for a mean duration of 101.9 ± 33.8 months (range, 4–209 months). The mean PFS was 94.5 ± 40.9 months (range 2–209 months), with the grade I, grade II and grade III 5-year PFS being 93.1%, 72.9% and 41.9%, respectively. The mean OS was 101.1 ± 34.2 months (range 4–209 months), with the grade I, grade II and grade III 5-year OS being 97.7%, 72.5% and 66.7%, respectively (Table 2). Among 39 deaths during the follow-up, 2 were due to reasons other than meningioma progression. One was due to sudden heart attack 32 months after surgery. The other mortality was due to accompanied breast cancer, 49 months after surgery.

Univariate and multivariate cox proportional survival analysis showed that older age (PFS, P = 0.026; OS, P = 0.000) and recurrent status (PFS, P = 0.000; OS, P = 0.000) were found to serve as independent prognostic factors for both worse PFS and OS. Higher histological grade was significantly associated with a shorter PFS (P = 0.0000, Log-rank test) and OS (P = 0.0000, Log-rank test), and served as an independent factor for shorter OS (P = 0.001). Loss of H3K27me3 staining (P = 0.037) and higher Ki-67 index (P = 0.002) were independent factors only for shorter PFS (Supplementary Table 1). We further performed stratified analysis based on H3K27me3 staining status. EOR was not associated with outcomes in both patients with negative H3K27me3 staining (PFS, P = 0.596; OS, P = 0.782) and in patients with postive H3K27me3 staining (PFS, P = 0.114; OS, P = 0.439). Post-operative radiation had no association with outcomes in patients with negative H3K27me3 (PFS, P = 0.966; OS, P = 0.836). However, post-operative radiation was associated with a better OS (P = 0.013), and not PFS (P = 0.099), in patients with postive H3K27me3.

We next performed survival analysis in 42 patients who received post-operative radiation according to the H3k27me3 methylation status. Twenty-four tumors had retained H3K27me3 and 18 tumors had its loss. No statistical difference of PFS [P = 0.117, HR (95% CI): 0.44 (0.16–1.22)] or OS [P = 0.508, HR (95% CI): 0.71 (0.16–1.22)] was identified, showing no correlation between H3K27me3 methylation status and resonpse to radiation.

Because histological grade impacted survival, all 192 patients were categorized into two groups based on tumor histological grades (low grade, WHO I; and high-grade, WHO II and III) for stratified survival analysis. Patients in

Table 2 Treatment and prognosis of 192 patients with parasagittal meningioma

Treatment and prognosis	Value	Treatment and prognosis	Value (%)
Extent of resection		Grade II	60.5
GTR	165 (85.9%)	Grade III	41.9
Simpson 1	100 (52.1%)	7-year OS by WHO Grade, months	
Simpson 2	65 (33.8%)	Grade I	93.9
STR	27 (14.1%)	Grade II	61.6
Simpson 3	7 (3.6%)	Grade III	61.9
Simpson 4	20 (10.4%)	7-year PFS in grade I	
Postoperative radiation therapy	42 (21.9%)	GTR only	94.7
Outcome at last follow-up		GTR + radiation	NA
Dead	39 (20.3%)	STR only	75.0
Alive and well	140 (72.9%)	STR + radiation	100
Recurrent	44 (22.9%)	7-year PFS in grade II&III	
Progression-free survival, months		Primary	79.4
3 year rate	88.4%	GTR only	62.5
5 year rate	83.6%	GTR + radiation	82.5
7 year rate	80.3%	STR only	66.7
Overall survival, months		STR + radiation	100
3 year rate	94.8%	Recurrent	11.1
5 year rate	89.1%	GTR only	10.1
7 year rate	83.8%	GTR + radiation	18.8
7-year PFS by WHO grade, months		STR only	NA
Grade I	91.6%	STR + radiation	0

WHO World Health Organization, *PFS* progression free survival, *OS* overall survival, *GTR* gross total resection, *STR* subtotal resection

each group were further divided into 4 groups based on EOR and subsequent adjuvant treatments.

For WHO grade I PMs, GTR was achieved in 116 patients, while STR achieved in the remaining 15 patients. More radical resection was significantly associated with a better PFS (P = 0.0229, log-rank test). However, no OS benefit was observed for GTR over STR (P = 0.2108) (Fig. 1). In addition, patients with STR did not benefit from adjuvant radiotherapy, in both PFS (P = 0.2146) and OS (P = 0.4038).

Among 61 high-grade PMs, 37 (60.7%) were newly diagnosed and 24 (39.3%) were recurrent PMs. The 7-year PFS and OS rate for patients with newly diagnosed high-grade PMs were 79.5% (95% CI, 61.6–89.7%) and 83.6 (95% CI, 67.1–92.3%), respectively; while for recurrent ones, the PFS and OS rate dropped dramatically to 11.9% (95% CI, 2.0–29.2%) and 29.2% (95% CI, 13.0–47.6%), respectively. Subsequent tumor recurrence occurred in 83.3% (20/24) of patients who presented with recurrent high-grade PMs, and 24.3% (9/37) of patients with newly diagnosed high-grade PMs. Patients with recurrent high-grade PMs have statistically shorter PFS (P = 0.0000, Log-rank test) and OS (P = 0.0000, Log-rank test) compared to newly diagnosed high-grade PMs (Fig. 2).

Newly diagnosed high-grade PMs were further divided into four groups according to EOR and postoperative radiotherapy, namely GTR only, GTR + radiation, STR only, and STR + radiation. No difference was observed in PFS (P = 0.4607) between the four groups. However, patients with post-operative radiation had a significantly longer OS than patients without radiation (P = 0.0129). No difference was observed between GTR and STR patients (P = 0.6541) (Fig. 3). In recurrent high-grade PM patients, there was a significant PFS difference among the four groups (P = 0.0288), with the longest PFS in patients receiving GTR + radiation. However, no OS difference was observed among the four groups (P = 0.9726) (Fig. 3).

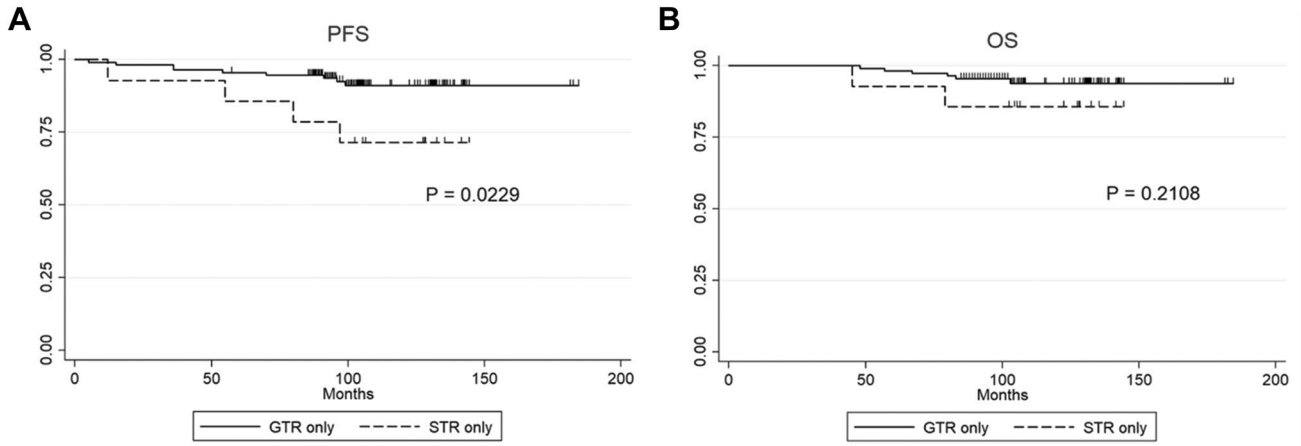

Fig. 1 Kaplan–Meier survival curves of WHO Grade I PM. **a** PFS and **b** OS of patients with WHO Grade I PM by extent of tumor resection

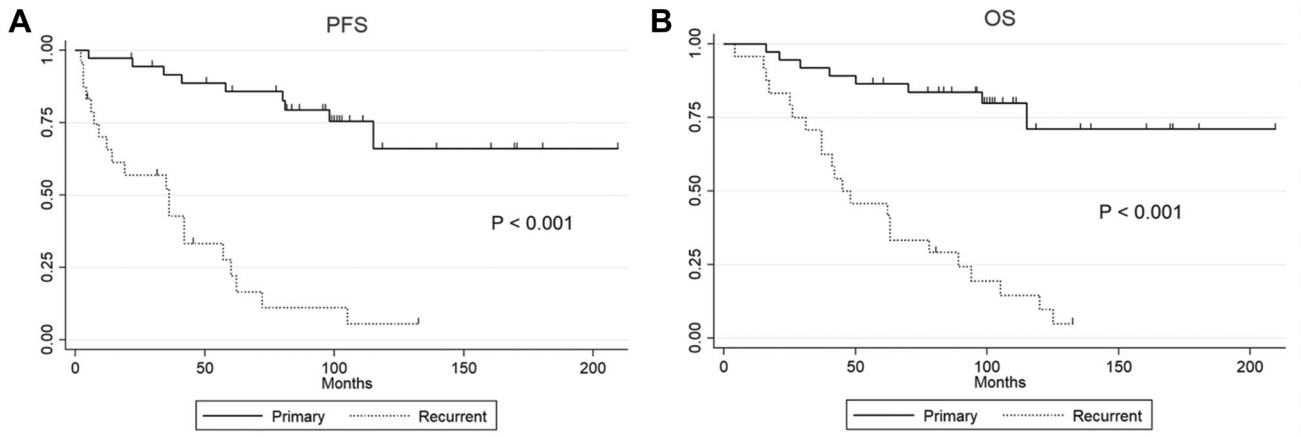

Fig. 2 Kaplan–Meier survival curves of WHO Grade II&III PM. **a** PFS and **b** OS of patients with WHO Grade II&III PM by tumor recurrent status

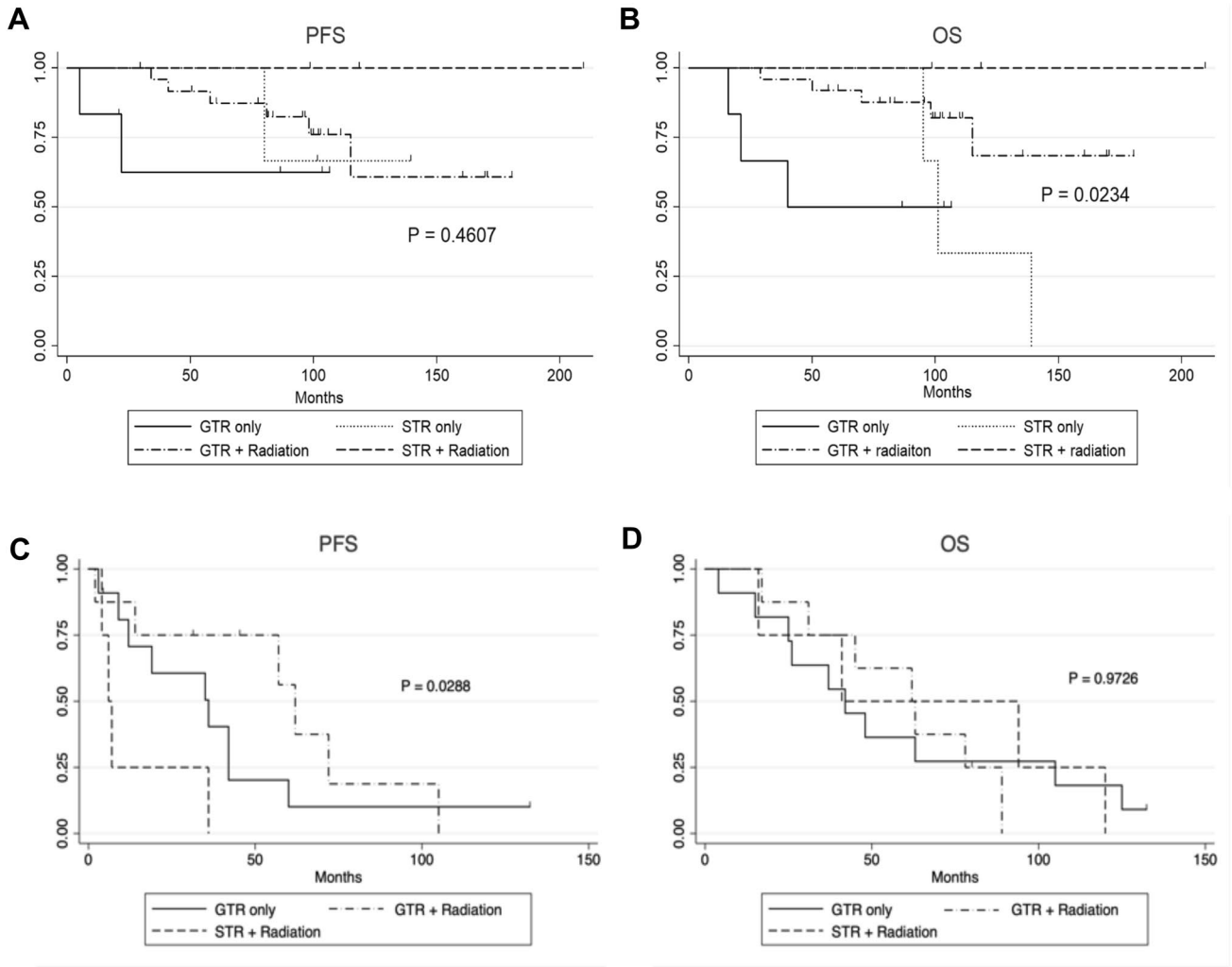

Fig. 3 Kaplan–Meier survival curves of high-grade de novo and recurrent PMs. **a** PFS and **b** OS of de novo WHO Grade II&III PMs by different treatment strategy. **c** PFS and **d** OS of recurrent WHO Grade II&III PMs by different treatment strategy. STR only group had only one patient and is not shown

Discussion

Treatment of parasagittal meningioma remains a formidable challenge in the field of neurosurgery. The role of radical resection and the utility of post-operative radiotherapy remains controversial due to diverse clinical and pathological characteristics of these tumors [6, 7, 9, 17]. In this study, we retrospectively investigated the clinical characteristics and long-term clinical outcomes of 192 patients with PM treated at a single neurosurgical center.

PMs were mostly grade I, constituting 68.2% in proportion. However, the proportion of high-grade meningioma was significantly higher than tumors at other locations, both in grade II and grade III [18, 19]. Studies have reported a correlation between meningioma locations and genetic, epigenetic background and radiomics' features [20, 21]. The difference in the distribution of histological grades propapbly reflects the distinct and characteristic genetic features of PM such as *NF2* loss.

Unlike previous studies, seizures, rather than headache, represent the most common presenting symptoms in our cohort [4, 5, 12, 22]. In addition, seizure attack was associated with a worse preoperative neurological function. However, seizure attack was not correlated with tumor grade, unlike the results reported by Hess et al. [23]. The high proportion of seizure attack at onset may be attributed to the involvement of eloquent brain areas, since all tumors in our series were adjacent to SSS.

Katz et al. reported that loss of H3K27me3 was associated with aggressive meningiomas and *NF2* mutations [14]. In our cohort, 16.7% of PMs showed negative H3K27me3 expression. We show that negative H3K27me3 was associated with malignant features, ie, higher tumor grade, tumor recurrent status and malignant transformation. In

the Katz's series of 232 meningiomas that included all intracranial locations, the proportion of H3K27me3 loss was significantly lower (10.8%) even though the cohort was enriched for WHO grade II tumors. The higher frequency of H3K27me3 loss in PMs may reflect a more aggressive biological behavior or NF2 alteration of PMs.

In our analysis of 192 patients with PM, the GTR rate was 85.9% and STR was 14.1%. The role of maximal tumor resection remains controversial [4, 6, 7, 9, 12, 24]. Interestingly, tumor with complete sinus invasion was more likely to achieve GTR than those with partial invasion in our cohort, since resection of tumors within patent sinus is more likely to induce venous damage and subsequent infarction. Balancing between complete tumor resection and controlled and safe surgery is a major clinical challenge. Most studies reported that aggressive surgical treatment was associated with a better survival and suggested a radical resection and sinus reconstruction. However, given the risk of surgical complications, adjuvant radiotherapy has been reported to be reasonable and beneficial [25–28].

Consistent with Brigitte Gatterbauer et al.'s opinion, the current work showed that PM should be viewed as a heterogeneous group of disease and multimodal treatment strategies should be applied based on distinctive tumor characteristics [4]. EOR, tumor grade, and tumor recurrent status should be considered for designing treatment strategies [7, 8, 29–31]. In grade I tumors, consistent with other studies, GTR was associated with a longer PFS. No difference in OS was observed, which may suggest the over 8-year follow-up period still not long enough for grade I tumors. Our study did not provide evidence for the benefit of adjuvant radiotherapy for patients with grade I PM. There were only 15 Grade I tumors that were subtotally resected, and rare recurrent events in this population and small patient numbers may have contributed to lack of statistical significance.

Consistent with our study, several studies on meningiomas at all locations have underlined a longer survival in de novo high-grade meningiomas compared to secondary or recurrent high-grade tumors [15, 16]. For high-grade tumors, the role of adjuvant radiotherapy after microsurgical resection remains undefined. Although Aizer et al. suggested no benefit of adjuvant radiotherapy for atypical meningiomas [32], many other studies reported otherwise [16, 33, 34]. Due to the observed prognostic difference, we analyzed primary and recurrent tumors separately to better define the role of treatments. In patients with high-grade de novo PM, GTR was not associated with a more favorable outcome. However, adjuvant radiotherapy brought an OS benefit to high-grade primary PMs, either with GTR or STR.

Patients with recurrent high-grade meningioma usually require additional surgery and eventually, adjuvant radiotherapy [35–37]. We show that patients with GTR and adjuvant radiotherapy had the best PFS, suggesting an influence of tumor resection and post-operative radiotherapy on PFS. Long-term outcome for recurrent high-grade PMs was dismal. Studies of all meningiomas have defined the role of GTR for recurrent high-grade meningiomas [38]. However, the effect of adjuvant radiotherapy is controversial. Studies including one from our own institution reported that adjuvant radiotherapy did not bring significant benefits to patients with high-grade meningioma [16]. In contrast, a retrospective study suggested better tumor control with the addition of radiation [33]. Notably, cases series in these studies include all locations, limiting the comparability with our study.

Limitations

Our study is a single institution, retrospective analysis. Due to still limited sample size of high-grade tumors, we clustered grade II and grade III into high-grade, which may have obscured heterogeneity in outcome potential present had the data been analyzed with distinct WHO grades.

Conclusion

Our study indicates that PMs have relatively high freqiuency of high-grade tumnors with aggressive biological behaviors. PMs should be viewed as a heterogeneous group of disease and distinctive tumor characteristics can be used to guide multimodal treatment strategies. Low-grade PM can benefit from radical resection. For high-grade primary PM, adjuvant radiotherapy but not EOR conferred difference in PFS.

Acknowledgements This study was supported by grants from the National Key R&D Program of China (2018YFC1312600, 2018YFC1312604 to Y. Gong), National Natural Science Foundation of China (81772674 to Y. Gong) and the Science and Technology Commission of Shanghai Municipality (18140900200 to Y. Gong).

Compliance with ethical standards

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

References

1. Holleczek B, Zampella D, Urbschat S, Sahm F, von Deimling A, Oertel J, Ketter R (2019) Incidence, mortality and outcome of meningiomas: a population-based study from Germany. Cancer Epidemiol 62:101562. https://doi.org/10.1016/j.canep.2019.07.001
2. Wang DJ, Xie Q, Gong Y, Mao Y, Wang Y, Cheng HX, Zhong P, Che XM, Jiang CC, Huang FP, Zheng K, Li SQ, Gu YX, Bao WM, Yang BJ, Wu JS, Xie LQ, Zheng MZ, Tang HL, Zhu

HD, Chen XC, Zhou LF (2013) Histopathological classification and location of consecutively operated meningiomas at a single institution in China from 2001 to 2010. Chin Med J 126:488–493
3. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS (2018) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. Neuro-Oncology 20:iv1–iv86. https://doi.org/10.1093/neuonc/noy131
4. Gatterbauer B, Gevsek S, Hoftberger R, Lutgendorf-Caucig C, Ertl A, Mallouhi A, Kitz K, Knosp E, Frischer JM (2017) Multimodal treatment of parasagittal meningiomas: a single-center experience. J Neurosurg 127:1249–1256. https://doi.org/10.3171/2016.9.jns161859
5. Sindou MP, Alvernia JE (2006) Results of attempted radical tumor removal and venous repair in 100 consecutive meningiomas involving the major dural sinuses. J Neurosurg 105:514–525. https://doi.org/10.3171/jns.2006.105.4.514
6. Brotchi J (2014) Should we pursue superior sagittal sinus grafting in parasagittal meningiomas in 2013? World Neurosurg 82:325–326. https://doi.org/10.1016/j.wneu.2013.07.107
7. Mantovani A, Di Maio S, Ferreira MJ, Sekhar LN (2014) Management of meningiomas invading the major dural venous sinuses: operative technique, results, and potential benefit for higher grade tumors. World Neurosurg 82:455–467. https://doi.org/10.1016/j.wneu.2013.06.024
8. Pettersson-Segerlind J, Orrego A, Lonn S, Mathiesen T (2011) Long-term 25-year follow-up of surgically treated parasagittal meningiomas. World Neurosurg 76:564–571. https://doi.org/10.1016/j.wneu.2011.05.015
9. Sindou M (2014) Meningiomas involving major dural sinuses: should we attempt at radical removal and venous repair? World Neurosurg 81:46–47. https://doi.org/10.1016/j.wneu.2013.07.119
10. Byard RW (2017) Parasagittal meningioma: a not so benign entity. Med Sci Law 57:175–178. https://doi.org/10.1177/0025802417732267
11. Gatterbauer B, Gevsek S, Höftberger R, Lütgendorf-Caucig C, Ertl A, Mallouhi A, Kitz K, Knosp E, Frischer JM (2017) Multimodal treatment of parasagittal meningiomas: a single-center experience. J Neurosurg 127:1249–1256. https://doi.org/10.3171/2016.9.JNS161859
12. Nowak A, Dziedzic T, Czernicki T, Kunert P, Marchel A (2014) Surgical treatment of parasagittal and falcine meningiomas invading the superior sagittal sinus. Neurol Neurochir Pol 48:174–180. https://doi.org/10.1016/j.pjnns.2014.05.003
13. Ricci A, Di Vitantonio H, De Paulis D, Del Maestro M, Gallieni M, Dechcordi SR, Marzi S, Galzio RJ (2017) Parasagittal meningiomas: our surgical experience and the reconstruction technique of the superior sagittal sinus. Surg Neurol Int 8:1–1. https://doi.org/10.4103/2152-7806.198728
14. Katz LM, Hielscher T, Liechty B, Silverman J, Zagzag D, Sen R, Wu P, Golfinos JG, Reuss D, Neidert MC, Wirsching HG, Baumgarten P, Herold-Mende C, Wick W, Harter PN, Weller M, von Deimling A, Snuderl M, Sen C, Sahm F (2018) Loss of histone H3K27me3 identifies a subset of meningiomas with increased risk of recurrence. Acta Neuropathol 135:955–963. https://doi.org/10.1007/s00401-018-1844-9
15. Hua L, Zhu H, Li J, Tang H, Kuang D, Wang Y, Tang F, Chen X, Zhou L, Xie Q, Gong Y (2018) Prognostic value of estrogen receptor in WHO Grade III meningioma: a long-term follow-up study from a single institution. J Neurosurg 128:1698–1706. https://doi.org/10.3171/2017.2.jns162566
16. Zhu H, Bi WL, Aizer A, Hua L, Tian M, Den J, Tang H, Chen H, Wang Y, Mao Y, Dunn IF, Xie Q, Gong Y (2019) Efficacy of adjuvant radiotherapy for atypical and anaplastic meningioma. Cancer Med 8:13–20. https://doi.org/10.1002/cam4.1531
17. Kondziolka D, Patel AD, Kano H, Flickinger JC, Lunsford LD (2016) Long-term outcomes after gamma knife radiosurgery for meningiomas. Am J Clin Oncol 39:453–457. https://doi.org/10.1097/coc.0000000000000080
18. Hua L, Zhu H, Deng J, Tian M, Jiang X, Tang H, Luan S, Wakimoto H, Xie Q, Gong Y (2018) Clinical and prognostic features of spinal meningioma: a thorough analysis from a single neurosurgical center. J Neuro-Oncol 140:639–647. https://doi.org/10.1007/s11060-018-2993-3
19. Kim JW, Jung HW, Kim YH, Park CK, Chung HT, Paek SH, Kim DG, Lee SH (2019) Petroclival meningiomas: long-term outcomes of multimodal treatments and management strategies based on 30 years of experience at a single institution. J Neurosurg. https://doi.org/10.3171/2019.2.jns182604
20. Coroller TP, Bi WL, Huynh E, Abedalthagafi M, Aizer AA, Greenwald NF, Parmar C, Narayan V, Wu WW, Miranda de Moura S, Gupta S, Beroukhim R, Wen PY, Al-Mefty O, Dunn IF, Santagata S, Alexander BM, Huang RY, Aerts H (2017) Radiographic prediction of meningioma grade by semantic and radiomic features. PLoS ONE 12:e0187908. https://doi.org/10.1371/journal.pone.0187908
21. Zhu Y, Man C, Gong L, Dong D, Yu X, Wang S, Fang M, Wang S, Fang X, Chen X, Tian J (2019) A deep learning radiomics model for preoperative grading in meningioma. Eur J Radiol 116:128–134. https://doi.org/10.1016/j.ejrad.2019.04.022
22. Colli BO, Carlotti CG Jr, Assirati JA Jr, Dos Santos MB, Neder L, Dos Santos AC (2006) Parasagittal meningiomas: follow-up review. Surg Neurol 66(Suppl 3):S20–S27. https://doi.org/10.1016/j.surneu.2006.08.023; **discussion S27–S28**
23. Hess K, Spille DC, Adeli A, Sporns PB, Brokinkel C, Grauer O, Mawrin C, Stummer W, Paulus W, Brokinkel B (2018) Brain invasion and the risk of seizures in patients with meningioma. J Neurosurg 130:789–796. https://doi.org/10.3171/2017.11.jns172265
24. Mathiesen T, Pettersson-Segerlind J, Kihlstrom L, Ulfarsson E (2014) Meningiomas engaging major venous sinuses. World Neurosurg 81:116–124. https://doi.org/10.1016/j.wneu.2013.01.095
25. Cho TH, Chung YG, Kim CY, Kim HK, Lee NJ, Chu JW, Choi MS (2000) Intraoperative radiation therapy as an adjunctive therapy for huge and highly vascular parasagittal meningiomas. J Korean Med Sci 15:718–723. https://doi.org/10.3346/jkms.2000.15.6.718
26. Pinzi V, Fariselli L, Marchetti M, Scorsetti M, Navarria P (2019) Stereotactic radiotherapy for parasagittal and parafalcine meningiomas: patient selection and special considerations. Cancer Manag Res 11:10051–10060. https://doi.org/10.2147/CMAR.S187371
27. Sasayama T, Nishihara M, Tanaka K, Mizukawa K, Ehara K, Kanomata N, Kohmura E (2008) Two metachronous tumors induced by radiation therapy: case report and review of the literature. J Neurooncol 88:315–320. https://doi.org/10.1007/s11060-008-9570-0
28. Shen H, Yu M, Tsoli M, Chang C, Joshi S, Liu J, Ryall S, Chornenkyy Y, Siddaway R, Hawkins C, Ziegler DS (2019) Targeting reduced mitochondrial DNA quantity as a therapeutic approach in pediatric high-grade gliomas. Neuro Oncol. https://doi.org/10.1093/neuonc/noz140
29. Boskos C, Feuvret L, Noel G, Habrand JL, Pommier P, Alapetite C, Mammar H, Ferrand R, Boisserie G, Mazeron JJ (2009) Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. Int J Radiat Oncol Biol Phys 75:399–406. https://doi.org/10.1016/j.ijrobp.2008.10.053
30. Girvigian MR, Chen JC, Rahimian J, Miller MJ, Tome M (2008) Comparison of early complications for patients with convexity and parasagittal meningiomas treated with either stereotactic radiosurgery or fractionated stereotactic radiotherapy. Neurosurgery 62:A19–A27. https://doi.org/10.1227/01.neu.0000325933.34154.cb; **discussion A18–A27**

31. Magill ST, Theodosopoulos PV, McDermott MW (2016) Resection of falx and parasagittal meningioma: complication avoidance. J Neurooncol 130:253–262. https://doi.org/10.1007/s11060-016-2283-x
32. Aizer AA, Arvold ND, Catalano P, Claus EB, Golby AJ, Johnson MD, Al-Mefty O, Wen PY, Reardon DA, Lee EQ, Nayak L, Rinne ML, Beroukhim R, Weiss SE, Ramkissoon SH, Abedalthagafi M, Santagata S, Dunn IF, Alexander BM (2014) Adjuvant radiation therapy, local recurrence, and the need for salvage therapy in atypical meningioma. Neuro-Oncology 16:1547–1553. https://doi.org/10.1093/neuonc/nou098
33. Choi Y, Lim DH, Jo K, Nam D-H, Seol HJ, Lee J-I (2014) Efficacy of postoperative radiotherapy for high grade meningiomas. J Neurooncol 119:405–412. https://doi.org/10.1007/s11060-014-1507-1
34. Durand A, Labrousse F, Jouvet A, Bauchet L, Kalamaridès M, Menei P, Deruty R, Moreau JJ, Fèvre-Montange M, Guyotat J (2009) WHO grade II and III meningiomas: a study of prognostic factors. J Neurooncol 95:367–375. https://doi.org/10.1007/s11060-009-9934-0
35. Valery CA, Faillot M, Lamproglou I, Golmard JL, Jenny C, Peyre M, Mokhtari K, Mazeron JJ, Cornu P, Kalamarides M (2016) Grade II meningiomas and Gamma Knife radiosurgery: analysis of success and failure to improve treatment paradigm. J Neurosurg 125:89–96. https://doi.org/10.3171/2016.7.gks161521
36. Wang C, Kaprealian TB, Suh JH, Kubicky CD, Ciporen JN, Chen Y, Jaboin JJ (2017) Overall survival benefit associated with adjuvant radiotherapy in WHO grade II meningioma. Neuro-Oncology 19:1263–1270. https://doi.org/10.1093/neuonc/nox007
37. Weber DC, Ares C, Villa S, Peerdeman SM, Renard L, Baumert BG, Lucas A, Veninga T, Pica A, Jefferies S, Ricardi U, Miralbell R, Stelmes JJ, Liu Y, Collette L, Collette S (2018) Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a phase-II parallel non-randomized and observation study (EORTC 22042–26042). Radiother Oncol. https://doi.org/10.1016/j.radonc.2018.06.018
38. Jamilson Araújo Pereira B, Nogueira de Almeida A, Pires H, de Aguiar P, Silva Paiva W, Jacobsen Teixeira M, Kazue Nagahashi Marie S (2019) Comprehensive analysis of meningioma in the first two decades of life: a systematic review. Neurochirurgie. https://doi.org/10.1016/j.neuchi.2019.10.007