Microcystic Meningioma Has A Worse Outcome Than Other WHO Grade 1 Subtypes

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Abstract

Objective: The aim is to evaluate the clinical, radiological features and long-term outcomes of microcystic meningiomas (MM) in a single neurosurgical center.

Methods: A total of 87 consecutive patients underwent surgical resection of MM between 2005 to 2016 were enrolled for analysis. Clinical, pathological, radiological and prognostic information was collected and analyzed; Univariate and multivariate COX analysis was conducted to select factors affected the progression-free survival (PFS). PFS was compared among other Grade 1 subtypes in our center as well.

Results: 56 females and 31 males were identified. 12 patients (13.8%) experienced tumor progression. The median PFS was unavailable, and the 5-, 10-, and 15-year PFS rates were 96.9%, 84.0%, and 73.9%, respectively. Peri-tumor brain edema (PTBE) was frequent in MMs (85%). Univariate COX analysis demonstrated that skull base location, STR, and higher Ki-67 were significant negative prognostic factors for PFS ($P < 0.05$), while tumor location and Ki-67 were independent factors ($P < 0.01$). MM had a worse prognosis when compared to other WHO Grade 1 subtypes diagnosed in our neurosurgical center during the same time period ($P = 0.0087$).

Conclusions: MM is a rare subtype of grade 1 meningioma, PTBE and reticular enhancement were characteristic in MMs. skull base location and higher Ki-67 labeling index were independent negative prognostic factors. MMs had a shorter PFS than the other WHO Grade 1 subtypes.

Introduction

Meningiomas are the most common primary tumors in the central nervous system and account for approximately 39% of all intracranial neoplasms [1]. According to the WHO grading standard in 2021, meningiomas can be classified into three grades and fifteen histological subtypes [2]. Approximately 80% of meningioma are WHO grade 1, which are usually benign and don't exhibit aggressive behaviors, among which, microcystic meningioma (MM), which was first named by Kleinman et al. in 1980, was included in the WHO grading standard in 1993 [3].

Microcystic meningioma is a rare subtype WHO 1 meningioma which only accounting for about 1.6% of the total meningiomas [4]. Like other Grade 1 meningiomas, MM was reported to show benign behaviors both clinically and histologically. MM often occurs in the supratentorial area. Common clinical manifestations are headache, seizure attack and contralateral weakness due to the tumor compression on brain tissue [5-7]. Histologically, MM shows vacuolation and microcapsule-like structure under the background of mucus, it is composed of star-shaped or fusiform cells arranged in a vortex shape, the intercellular structure is loose and the cytoplasm is vacuolar [8]. The radiological characteristics of some MM patients are not typical and usually difficult to distinguish from other intracranial neoplasms like atypical meningioma or glioma [9]. Recently, studies showed the molecular genetic characteristics of MM are represented by the amplification of chromosome 5[10], which gives us a hint that MM could be special lesions different from the other grade I meningiomas. Up to now, very few studies

comprehensively studied clinical, radiological and prognostic characteristics of this relatively rare subtype of tumor. In this study, we collected 87 consecutive patients with MM in a single neurosurgical center to evaluate the clinical, radiological features and long-term outcomes of MM. We also compared the outcomes among the different grade 1 histological subtypes.

Materials And Method

Patient and clinical information

This study included 87 consecutive patients underwent surgery between 2005 to 2016 in the Huashan Neurosurgical Center. The inclusion criteria were as follows: a) patients with complete clinical and histopathological data in our hospital, b) patients underwent a full follow-up at least for five years, c) patients underwent initial tumor resection surgery, d) patients were pathologically diagnosed with MM. The pathological diagnosis was reviewed by two experienced neuro-pathologists according to the criteria of 2016 WHO classification of meningiomas. The following clinical information was extracted from the medical records: gender, age of diagnosis, location, clinical manifestations, symptom duration and extent of resection. This study was approved by the Human Subjects Institutional Review Board of Huashan Hospital.

Radiological Data

The features of magnetic resonance images (MRI) were evaluated by two experienced radiologists, both blinded to clinical and histopathological findings. The radiological data including T1WI, T2WI, FLAIR, enhanced T1WI was collected. The following features were investigated and analyzed: tumor size, Cystic formation, Dural tail sign, peritumoral brain edema (PTBE), heterogeneous enhancement, Marginal and reticular enhancement. Tumor size was computed as the measurement of maximal diameter based on MRI. PTBE was evaluated with T2WI sequence and divided into four levels, namely absent (edema index [EI]<0.01), mild ($0.01 < EI < 0.50$), moderate ($0.51 < EI < 1.99$), and severe ($EI \geq 2.0$).

Immunohistochemical Results

All surgical specimens were reviewed and re-confirmed by two board-certified neuro-pathologists (Dr. Y Wang and Dr. HX Chen) according to the 2016 WHO meningioma grading criterion. "Brain invasion" was excluded for all patients enrolled. EMA, Vim, PR and Ki-67 immunohistochemistry was used as routine diagnostic markers in our center, which were reviewed as well.

Follow Up

Patients were followed up through phone or out-patient service after surgery according to the meningioma follow-up criterion in our center [11]. The last follow-up was in October 30, 2021. Postoperative complications, progression-free survival and postoperative treatment were recorded. Recurrence was confirmed with the enhanced T1WI MR images. PFS was defined as the time between surgery and tumor progression. Thirty patients were lost during the follow-up, and the remaining 87 patients were included in the final analysis.

A total of 527 patients with other histological subtype grade 1 meningiomas operated during the same time period whose follow-up data were available were enrolled for PFS comparisons.

Statistical analysis

Statistical analysis was performed using R software (Version 3.4.1). Student's t-test and Mann-Whitney U test compared continuous and categorical variables, respectively. Kaplan–Meier method and the long-rank test was used to evaluate PFS. Univariate and multivariate Cox regression analysis was used to select independent predictors of MM progression. A two-sided P-value < 0.05 was defined as statistically significant.

Result

Clinical characteristics

A total of 13657 patients with meningioma underwent surgery in Huashan Neurosurgical Center between 2005 to 2016 were initially identified, among which, 117 cases were MMs, accounting for 0.86% of all meningiomas cases in our center. 87 MM patients (31 males and 56 females) with detailed follow-up information were enrolled for final analysis. The overall mean age was 51.82 ± 11.36 years (range, 28 - 79 years), while the mean age of males was 49.58 ± 11.57 years (range, 28 - 79 years) and that of females was 53.05 ± 11.57 years (range, 32 - 78 years). No significant difference of age was observed between male and female genders ($p = 0.173$). Convexity was the most common location (62, 71.3%), followed by skull base (14, 16.1%) and parasagittal/falx (11, 12.6%). Tumor location was classified as non-skull base and skull-base for further survival analysis. The most common symptom was headache (44, 50.5%), other manifestations included contralateral weakness and numbness (19, 21.8%); seizure attack (7, 8.0%); visual disturbance (5, 5.7%); facial paralysis (3, 3.4%); speech disturbance (2, 2.3%); memory loss (2, 2.3%). Five patients were (5.7%) asymptomatic. The mean symptom duration was 9.00 ± 18.40 months (range, 0.25 - 120 months). Simpson grade I, II, III, and IV resection was achieved in 61, 19, 6, and 1 patient, respectively (Table 1). Skull base tumors were more likely to achieve STR resections ($p = 0.013$). The potential continuous prognostic variables were converted to binary categorical variables via the receiver operation curve (ROC), and the optimal cut-offs of age, Ki-67, and Karnofsky Performance Status (KPS), were 58.5 years old, 3.5% and 70, respectively (Supplementary Fig 1).

Histopathology

EMA and Vim were positive in all the cases. PR was positive in 36 patients (41.38%), weak positive in 13 patients (14.94%), and negative in 38 patients (43.68%). The median Ki-67 labeling index was 2% (range 0% - 5%). Ki67 was 0% in 17 cases, 1% in 29 cases, 2% in 16 cases, 3% in 17 cases, 4% in 4 cases and 5% in 4 cases. No patients' Ki-67 labeling index was higher than 5% (Table 1).

Radiological features

Radiological features were analyzed in 40 patients (46.0%) whose MRI images were available. The mean tumor size was 4.2 ± 1.2 cm (range 1.6cm - 6.8cm). Among which, 31 patients' (77.5%) MRI manifested as solid, 9 patients' tumors (22.5%) had cystic formations. Dural tail signs were apparent in 29 cases (72.5%). On T1 sequence, 35 tumors (87.5%) presented with hypointense and 5 tumors (12.5%) manifested with isointense to grey matter. On T2 sequence, all the cases presented with hyperintense. On T1 enhanced sequence, 22 tumors (55%) showed strong homogeneous enhancement, 7 tumors (17.5%) showed heterogenous enhancement and 11 tumors (12.6%) showed Marginal and reticular enhancement (Supplementary Fig 3). PTBE was present in 34 patients (85%), as mild in 11 patients (27.5%), moderate in 13 patients (32.5%), and severe edema in 10 patients (25%) (Table 2).

Long-term Follow-up outcomes

The last follow-up data was October 30, 2021. The mean follow-up period was 101.66 ± 40.92 (range, 53 - 192 months). The median KPS score of the last follow-up was 90 (range 50-100). Postoperative KPS score was improved in 65 cases (74.7%), deteriorated in 3 cases (3.4%) and unchangeable in 19 cases (21.8%). There was a significant improvement of KPS score after tumor resections ($p < 0.001$). No patient except one with Simpson grade IV resection received post-operative gamma-knife therapy. Two patients died during the follow-up due to other reasons, one was from Pancreatic cancer and the other one died of natural cause. Twelve patients (13.8%) experienced recurrences during the follow-up, among which, five patients under STRs and 7 under GTRs. The median PFS was unavailable, and the 5-, 10-, and 15-year PFS rates were 96.9%, 84.0%, and 73.9%, respectively. The median OS was unavailable since no patient died of tumor progression during the follow-up (Table 2).

All clinical characteristics, including age, gender, tumor location, extent of tumor resection, Ki-67, PR, symptom duration and preoperative KPS score, were analyzed as prognostic factors via univariate and multivariate Cox regression analyses. In the Pearson Correlation Test, all correlation coefficients were below 0.6, indicating these variables were independent (Supplementary Fig 2a). Univariate COX analysis demonstrated that non-skull base location, GTR, and lower Ki-67 labeling index were significant factors associated with longer PFS (Fig 1). Multivariate Cox regression analysis confirmed that Ki-67 labeling index (hazard ratio (HR) =29.69, 95% confidence interval [1.56~192], $P<0.001$) and tumor location (hazard ratio (HR) = 7.66, 95% confidence interval [1.04~56.4], $P=0.046$) were independent prognostic factors affecting PFS (Table 3).

PFS comparison among WHO grade 1 meningiomas.

From 2003 to 2018, follow-up information of 527 patients with different WHO 1 subtype meningiomas (excluding MMs) were available in our center. These 527 Grade 1 meningiomas included 93 angiomatous, 149 psammomatous, 97 meningothelial, and 188 fibrous subtypes, with recurrences in 4 (4.3%), 7 (4.7%), 3 (3.1%), and 9 (4.8%) individuals, respectively. Median PFS was also unavailable in these tumors, with the 5-10- and 15 year PFS rate as 98.79%, 96.33% and 91.11% respectively. PFS of MM was significantly poorer than the other WHO Grade 1 subtypes ($P < 0.001$). No significant PFS difference was observed among these subtypes excluding MMs ($P = 0.9$). (**Fig 2a - b**). No difference on extent of resection rate ($P = 0.63$) or Ki-67 labeling index ($P = 0.21$) was observed between MMs and other grade 1 histological subtypes (**Supplementary Fig 2b**). In order to evaluate the influence of extent of resection on PFS difference between MM and the other subtypes, survival analysis was performed in patients with GTR only. Results showed that in patients with GTR, MM still had a worse PFS than the other subtypes ($P = 0.047$). Individual subtype analysis showed no significant difference on PFS was observed among meningioma subtypes excluding MMs ($p = 0.99$), excluding the impact of extent of resections on the PFS difference (**Fig 2c - d**).

Discussion

Microcystic meningioma is a relatively rare subtype of WHO Grade 1 meningioma [4]. The clinical, radiological, and genetic characteristics of MMs are still not clear due to the limited number of patients. Studies concerning MMs are either case reports or small case series [8, 12-16]. Our study comprehensively analyzed the clinical, radiological and prognostic characteristics in 87 MM patients in our neurosurgical center. To the best of our knowledge, this is the largest MM series from a single academic institution. In this series from 2005 to 2016, the incidence of MM was about 0.86%, which is similar to previous studies [6]. MM is usually characterized by the onset of slow progressive symptoms due to the compression of adjacent structures[17]. In our study, the most common symptoms were headache, contralateral weakness, and seizure attack. The mean age of patients in our series was 51.8 years, which is similar to other benign meningiomas. The female/male ratio of our patients was 1.81, which is in accordance with meningiomas in general but higher than previous series[3, 6, 7]. The most common locations of MM were convexity and parasagittal/falx, which is also in accordance with previous studies [6, 13, 18]. GTR could be achieved in most patients. For the small proportional patients with STR, few were recommended to take adjuvant radiotherapies, in our series, only one patient with Simpson grade IV resection was recommended to gamma knife radiotherapy, long-term follow-up through radiological examinations was recommended for these patients [19, 20].

Radiological analysis showed severe PTBE was not uncommon in MMs [6, 21, 22]. In our series, as many as 34 cases (85%) had different degrees of PTBE. The reticular enhancement was considered as the unique radiological presentation of MM in several studies [22-24], but its sensitivity was not satisfying [6, 13]. There were only 3 patients presented with this character in our cohort. Lin et al. divided microcystic meningiomas into three types according to their imaging and clinical features in their series of 69 patients.[25] These three types of microcystic meningiomas were significantly different in sex ratio, severe PTBE incidence and intraoperative tumor resection extent. In our series, the statistical analysis of

the correlation between radiological presentation and clinical features was limited since over half (47/80) radiological data of patients were unavailable.

The genetic background of MM is still not clear. There were few studies about the molecular genetic analysis of MM. The common genetic changes include NF2, TRAF7, KLF4, AKT1, SMO and POLR2A mutations which is frequent in other grade 1 meningioma was not frequent in MMs [26-28]. Ketter et al. recently detected 16 cases of hyper-diploid meningioma in 667 consecutive patients, of which 6 cases were microcystic meningioma, indicating a potential hyper-diploid feature of MMs [29]. In our series, molecular data was unavailable. Molecular characteristics of MMs warranted further investigations.

In the studies reported by Lin et al. and Kalani et al., extent of resection was significantly associated with outcome [3, 6]. Our survival analysis demonstrated that other than extent of resection, tumor location and Ki-67 labeling index were also associated with PFS. Skull-base location and higher Ki-67 labeling index were independent risk factors for shorter PFS.

An interesting phenomenon is that, in our series, MM has a worse outcome than other WHO 1 meningiomas, with as many as 12 patients (13.8%) experienced tumor progression. The 5-, 10- and 15-year PFS rate of MM was all lower than non-MMs. Two possible factors (Ki-67 labeling index and extent of tumor resection) that could lead to the progression survival difference was evaluated in our own series. No ki-67 difference was observed between MMs and other grade 1 tumors. Even in patients with GTR, MMs still have a significant worse outcome than other grade 1 subtypes, indicating a distinct post-surgery natural history of MM. We also made a mini-review incorporating studies concerning the outcome of grade 1 meningiomas. Outcomes between MMs and other grade 1 subtypes was evaluated. Interestingly, MMs tended to have a worse outcome than other subtypes. Prognostic information of MM was only available in two studies, showing a recurrent rate of 12% and 1.6%, respectively. However, the follow-up time was not long enough for the 1.6% recurrent rate reported by Lin et al., with only a median of 49 months. While in six other studies focusing on other subtypes of grade 1 meningiomas, the recurrent rate ranged from 1.54% - 13.3%, which all was lower than that of MMs in our series (Supplementary Table 1), indicating a distinct post-operative nature history of MMs[3, 25, 30-35]. Therefore, longer-term and close follow-up should be recommended for MM patients [20]. The reason that MMs had a worse outcome than other subtypes warranted further investigations.

Limitations

The main limitations of this study including two aspects. Firstly, the radiological data of 47 patients were lost, the radiological characteristics were difficult to summarize. Secondly, survival information was not available in all subtypes, we still lack data of secretory, translational, lymphoplasmacyte-rich and metaplastic subtypes, inclusion of all the grade 1 subtypes will make our conclusion more convincing.

Conclusions

MM is a rare subtype of grade 1 meningioma, PTBE and reticular enhancement were characteristic in MMs. skull base location and higher Ki-67 labeling index were independent negative prognostic factors. MMs had worse outcome than other WHO Grade 1 meningiomas, subgroup analysis showed even in patients with GTR, PFS of MM is still worse.

Abbreviations

WHO = world health origination; MM = microcystic meningioma; PFS = progression-free survival; PTBE = peri-tumor brain edema; STR = subtotal resection; GTR = gross total resection; MRI = magnetic resonance images; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; FLAIR = fluid attenuated inversion recovery; EI = edema index; EMA = epithelial membrane antigen; Vim = vimentin; PR = progesterone receptor; ROC = receiver operation curve; KPS = Karnofsky performance status; HR= hazard ratio; AM = angiomatous meningioma; PM = psammomatous meningioma; MeM = meningothelial meningioma; FM = fibrous meningioma.

Statements & Declarations

Previous Presentation: This manuscript has not been published previously and is not under consideration elsewhere in any language in whole or in part.

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Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request

Ethics approval: This clinical study was approved by the Human Subjects Institutional Review Board at Huashan Hospital, Fudan University

Consent to participate: Informed consent was obtained from all individual participants included in the study

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in **Supplementary Fig 3. a-h**.

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Tables

Table1. Clinical characteristics of microcystic meningioma

Characteristics	Value	Percentage (%)
Gender		
Male	31	35.6
Female	56	64.4
Age, years		
Male	49.58 ± 11.57	
Female	53.05 ± 11.15	
total	51.82 ± 11.36	
Location		
Convexity	62	71.3
Parasagittal	7	8.0
Sphenoid ridge	5	5.7
Flax	4	4.6
Petro clival	2	2.3
Tentorial	2	2.3
Olfactory	2	2.3
Middle skull base	2	2.3
Sella region	1	1.2
Clinical symptoms		
Headache	44	50.5
Contralateral weakness	19	21.8
Seizer attack	7	8.0
Visual disturbance	5	5.7
Asymptomatic	5	5.7
Facial paralysis	3	3.4
Speech disturbance	2	2.3
Memory loss	2	2.3
Symptom duration (month)	9.01±18.40	0.25-120
Extent of tumor resection		

Simpson I	61	70.1
Simpson II	19	21.84
Simpson III	6	6.90
Simpson IV	1	1.15
Preoperative KPS	82.99 ± 11.63 [30 - 100]	
Post-operative KPS	93.79 ± 9.92 [50 - 100]	
Ki-67	1.70% ± 1.36% [1% - 5%]	
PR		
Positive	36	41.38
Weak positive	13	14.94
Negative	38	43.68

KPS, Karnofsky Performance Score; PR, Progesterone Receptor

Table 2. Radiological features of microcystic meningioma

Characteristics	Value	Percentage (%)
Tumor size	4.2 ± 1.19 [1.6 - 6.8]	
Cystic formation	9	22.5
Dural tail sign	29	72.5
PTBE		
None	6	15
Mild	11	27.5
Moderate	13	32.5
severe	10	25
Signal on T1		
Hypointense	35	87.5
Isointense	5	12.5
Signal on T2		
Isointense	0	0
Hyperintense	40	100
T1+C		
Heterogeneous enhancement	22	55
Heterogeneous enhancement	7	17.5
Marginal and reticular enhancement	11	27.5
Radiological classification		
I	29	72.5
II	8	20
III	3	7.5
Mean follow-up, months	101.66 ± 40.92 (range, 5.3 - 192)	
Postoperative KPS	93.79 ± 9.92 [50 - 100]	
Improvement	61	70.11
Deterioration	6	6.90
No change	20	22.99
Recurrence	12	10.5

PFS rate	104.53 ± 40.57
5-year PFS	96.55
10-year PFS	89.66
15-year PFS	86.21

PTBE, peri tumor brain edema; KPS, Karnofsky Performance Score; PFS, progression free survival

Table 3. The univariate and multivariate COX regression analysis results.

Characters	Univariate COX analysis		Multivariate COX analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Gender	0.602 (0.1939-1.869)	0.370		
Age	3.773e-09 (0-Inf)	0.079*		
Tumor location	5.772 (1.813-18.38)	<0.001***	7.66(1.04-56.4)	0.046**
Resection range	7.121 (2.245-22.59)	<0.001***	2.65(0.49-14.4)	0.3
Ki-67	8.145 (2.017-32.9)	<0.001***	29.6(1.56-192)	<0.001***
PR	0.8915 (0.4846-1.64)	0.750		
Symptom duration	1.727 (0.5559-5.366)	0.340		
Preoperative KPS	0.4895 (0.1061-2.258)	0.350		

Figures

Figure 1

Kaplan-Meier survival curves. **a**: PFS of patients by Ki-67 labeling index. **b**: PFS of patients by the extent of tumor resection. **c**: PFS of patients by tumor location.

Figure 2

Kaplan-Meier survival curves. **a**: PFS in MM and other WHO Grade 1 meningiomas. **b**: PFS in angiomatous, psammomatous, meningothelial and fibrous subtypes. **c**: PFS in microcystic meningioma

and other WHO Grade 1 meningiomas with GTR. **d:** PFS in angiomatous, psammomatous, meningothelial and fibrous meningiomas with GTR.

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