Clinical Predictors of WHO Grades, Subtypes, and Atypical Histopathological Features of Meningiomas

Inthira Khampalikit MD*,
Pornsuk Cheunsuchon MD**, Bunpot Sitthinamsuwan MD*

** Division of Neurosurgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *WHO grade I meningiomas usually have an indolent course, while high-grade (grades II to III) tumors are associated with a more aggressive natural course.*
Objective: *To investigate clinical predictors of WHO grade, subtype, and atypical features of meningiomas.*
Material and Method: *Correlations between clinical variables and WHO grades, meningioma subtypes, atypical features of tumor, brain invasion, degree of connective tissue content, and microscopic calcification were analyzed.*
Results: *Of 233 meningiomas, 196 (84.1%) and 37 (15.9%) were WHO grade I and II, respectively. There were no WHO grade III tumors in the present study. Factors associated with a possibility of WHO grade II meningioma included younger age (p = 0.025), larger tumor size (p = 0.005), peritumoral brain edema (p = 0.001), and isosignal intensity of tumor on T2WI (p = 0.011) and FLAIR image (p<0.001). Hyposignal and hypersignal tumors on T2WI were correlated with transitional and meningothelial subtypes, respectively (p = 0.001). Meningiomas with soft consistency were likely to be fibrous subtype and associated with a low level of connective tissue. Radiographic predictors of atypical histopathologic features were presence of cystic component, peritumoral edema, bony erosion and absence of CFS cleft between tumor and brain, and homogeneous enhancement of tumor on T1WI. Tumor isosignal intensity on T2WI and FLAIR images could forecast the appearance of atypical features and brain invasion in histopathology. Small size, spinal location, and hyposignal intensity of tumors on T2WI were correlated with dense microscopic calcification.*
Conclusion: *Various clinical factors can be used to predict high-grade meningioma, tumor subtype, and microscopic atypical features - all of which are useful in tumor management.*

Keywords: *Meningioma, WHO grades, Subtypes, Atypical features, Connective tissue content, Calcification*

J Med Assoc Thai 2017; 100 (Suppl. 3): S122-S132
Full text. e-Journal: *http://www.jmatonline.com*

Meningioma is the most common benign primary tumor of the central nervous system[1]. Tumors can be categorized histopathologically into World Health Organization (WHO) grades I, II, or III[2]. Of these, WHO grade I meningiomas are benign and most commonly found. Meningioma can be treated with surgery, external beam radiation, or a combination of these two treatments[3]. Meningiomas with WHO grade II or III histology are regarded as high-grade meningiomas which have a higher risk of recurrence following treatment and are associated with lower overall survival[3-5]. Pathological criteria for diagnosing high-grade meningioma are histological appearances and atypical features, including small cell formation, hypercellularity, sheet-like growth, necrosis, prominent nucleoli and mitosis, and brain invasion[2]. A number of meningiomas are classified as WHO grade I, but they have some components of atypical features that do not fulfil the criteria of high-grade meningioma.

This study set forth to investigate the clinical factors that correlate with atypical histopathological features of meningioma. These predictors may be helpful in the pre-operative or intra-operative recognition of high-grade tumors, facilitating their exclusion from wait-and-see therapy or radiation treatment alone.

Correspondence to:
Khampalikit I, Division of Neurosurgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: +66-2-4198003, Fax: +66-2-4113006
E-mail: khampalikit@gmail.com

Material and Method

Study design

Cross-sectional study.

Population

All patients with intracranial or spinal meningiomas who underwent tumor resection at our institute from January 2007 to December 2011 were enrolled. All recruited cases had meningiomas originating from the virgin sites that had never been operated upon or treated by radiation. Clinical, neuroimaging, and intra-operative data were collected and analyzed. In all cases, histologic sections were reviewed by a neuropathologist (PC). Tumors were graded according to WHO classification. The protocol for this study was approved by Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

Data collection

Collected data comprised gender, age, duration of neurologic symptoms before surgery, tumor location, tumor characteristics on neuroimaging studies, and intraoperative tumor consistency. Clinical data were obtained from outpatient and inpatient records. Features on neuroimaging studies included tumor calcification on non-contrast enhanced computerized tomography (NCECT), tumor size, evidence of vasogenic brain edema, cystic component within the tumor, hyperostosis or bony erosion of the tumor base, en plaque appearance, cerebrospinal fluid (CSF) cleft between the tumor and brain, and signal intensity of meningioma on T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), and fluid-attenuated inversion recovery (FLAIR) imaging. Tumor signal intensity on MRI sequences was stratified into hypersignal, isosignal, and hyposignal intensities, when compared to that of neural gray matter. We also studied pattern of tumor enhancement (homogeneous or heterogeneous) on contrast-enhanced computerized tomography (CECT) and T1WI after injection of contrast media.

Intra-operative tumor consistency was obtained by operating neurosurgeons that used the grading system developed and reported in our previous study[6] (Table 1). Tumor grades and subtypes were classified using WHO criteria for classification of meningioma[2]. In cases that atypical features including small cell formation, hypercellularity, necrosis, prominent nucleoli, mitosis, and brain invasion were present (Fig. 1), each criteria was recorded. Degree of connective tissue content and calcification within the tumors were evaluated. Degree of connective tissue content was graded according to percentage of overall tumor section area as follows: low (<30%), moderate (30 to 60%), and high (>60%) (Fig. 2A-C). Degree of calcification was classified according to the 3 following levels: no calcification, low calcification (presence of calcification <50% of overall area), and high calcification (presence of calcification >50% of overall area) (Fig. 2D-F). Some data were unavailable in a number of cases; as such, the number of cases (n) for each individual parameter varied.

Statistical analysis

The data set was analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Inc., Chicago, IL, USA). One-way ANOVA was used to compare age and tumor size between groups. Pearson's Chi-square test and Fisher's exact test were used to investigate correlations between variables and pathological features. Data are presented as number or mean $\pm$ SD. Strength of association was evaluated and presented as odds ratio (OR) and 95% confidence interval (95% CI). The statistically significant level was defined as $p<0.05$.

Table 1. Classification of intraoperative meningioma consistency based on effectiveness of tumor resection performed using conventional neurosurgical tools and methods[6]

Grade	Consistency	Description
I	Soft	Meningioma can be removed using suction cannula for more than 80% of resected tumor volume
II	Intermediate	Meningioma can be removed using suction cannula for less than 80% of resected tumor volume OR Meningioma can be removed using ultrasonic aspirator for more than 80% of resected tumor volume
III	Hard	Meningioma cannot be removed using suction cannula OR Meningioma can be removed using ultrasonic aspirator for less than 80% of resected tumor volume OR Sharp surgical instrument, such as scalpel, surgical scissors, or loop monopolar electrocautery, is required for tumor resection

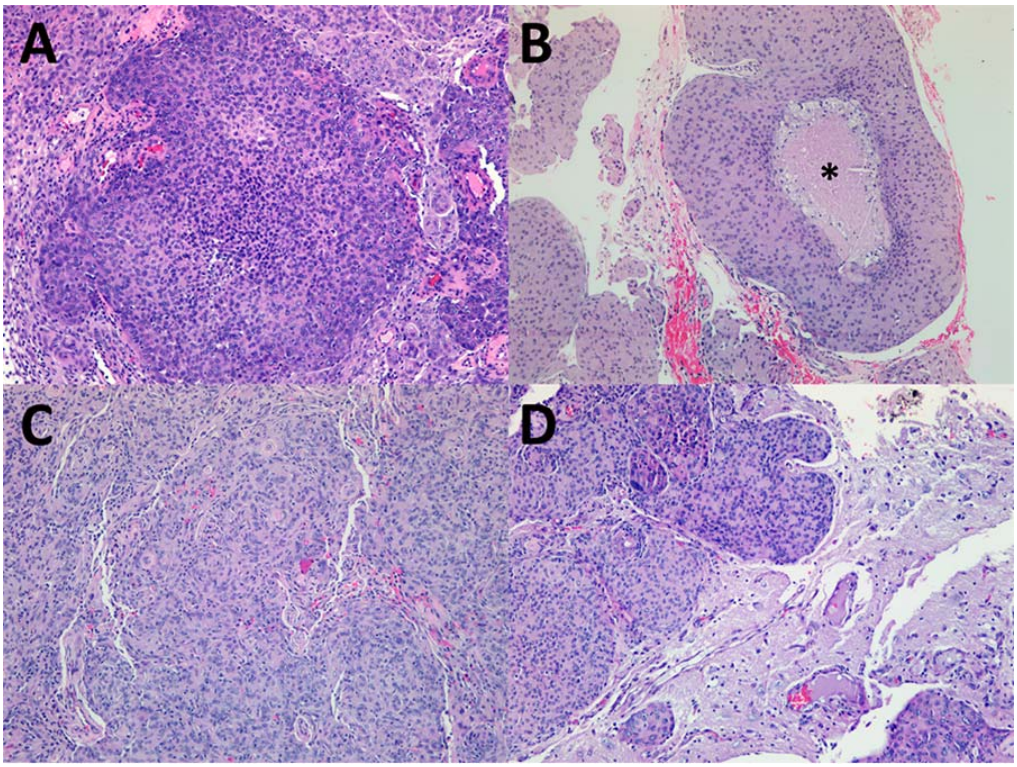

Fig. 1 Histologic features of atypical meningioma; (A) tumor showing increased cellularity and small cell formation with high nucleus/cytoplasm ratio (center); (B) spontaneous micronecrosis (asterisk); (C) prominent round nucleoli in numerous tumor cells; (D) brain invasion as tongue-like projection of tumor cells into brain parenchyma without intervening leptomeninge (hematoxylin and eosin stain, x100).

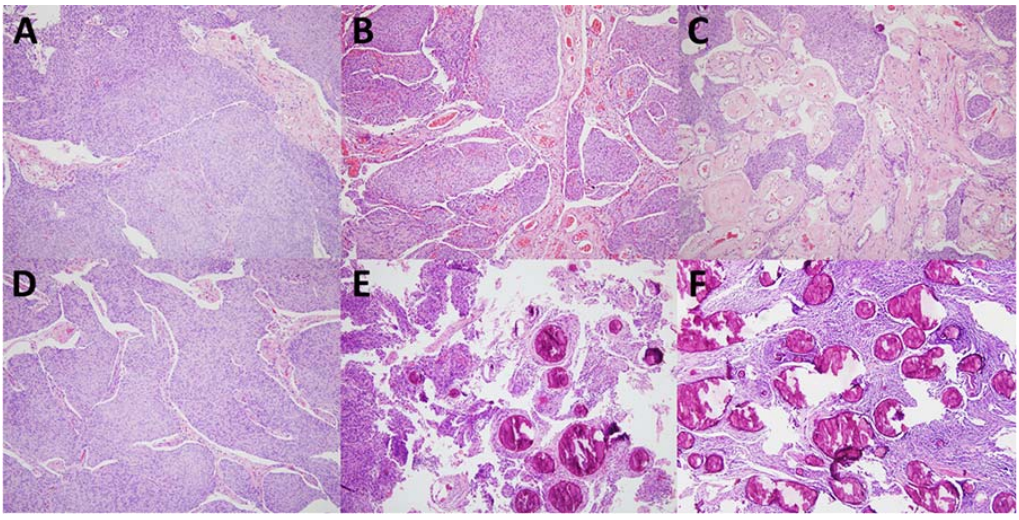

Fig. 2 Degree of connective tissue content (A-C) and calcification (D-F) of meningiomas; (A) low connective tissue content (<30% of HPF); (B) moderate connective tissue content (30 to 60% of HPF); (C) high connective tissue content (>60% of HPF); (D) no calcification; (E) low calcification (presence of calcification <50% of HPF); (F) high calcification (presence of calcification >50% of HPF).

Results

Demographic characteristics

Two hundred and twenty-three meningiomas were enrolled into the study. There were 199 (85.4%) females and 34 (14.6%) males, with a mean age of 50.7±12.8 years (range: 12-85). The most common location was sphenoid ridge (32 cases, 13.7%), followed by cerebral convexity (28 cases, 12%) and anterior clinoid process (27 cases, 11.6%) (Table 2). Mean tumor size was 4.3±1.8 cm (range: 0.8-10).

For histopathology, WHO grade I and II meningiomas were 196 (84.1%) and 37 (15.9%), respectively (Table 3). No WHO grade III meningiomas were identified in this study. The most common pathological subtype was meningothelial meningioma. Tumors that did not completely satisfy WHO grade II meningioma criteria were diagnosed as WHO grade I meningioma. Atypical features were found in both WHO grade I and II meningiomas. Cases with atypical features who met the diagnostic criteria of atypical meningioma were diagnosed as atypical meningioma. Meningiomas showing brain invasion were classified as WHO grade II meningioma, brain-invasive subtype[2]. From 233 studied cases, atypical features were identified, as follows: small cell formation (43 cases, 18.5%), hypercellularity (45 cases, 19.3%), necrosis (31 cases, 13.3%), prominent nucleoli (11 cases, 4.7%), mitosis >4 per HPF (2 cases, 0.9%), and no cases with sheet-like growth pattern. Brain invasive pattern was found in 19 (8.2%) of total cases, accounting for 51.4% of WHO grade II tumors.

From the correlation analysis between collected parameters and WHO grades and meningioma subtypes, we made the following observations (Table 4):

Mean age of WHO grade II group (46.4 years) was significantly younger than that of patients with WHO grade I tumors (51.5 years) ($p = 0.025$).

Mean tumor size of WHO grade II tumors (5.1±1.5 cm) was significantly larger than that of WHO grade I meningiomas (4.1±1.8 cm) ($p = 0.005$).

Tumors with peritumoral vasogenic edema were 5.8 times more likely to be WHO grade II meningiomas than tumors without vasogenic edema (95% CI: 1.95-17.51; $p = 0.001$).

Tumors showing isosignal intensity on T2WI and FLAIR imaging were more likely to be grade II than I ($p = 0.011$), whereas hypersignal meningiomas on both MRI sequences were more likely to be grade I than II ($p<0.001$).

Table 2. Tumor location

Tumor location	Number (%)
Supratentorial	**166 (71.2)**
Sphenoid ridge	32 (13.7)
Cerebral convexity	28 (12)
Tuberculum sellae	27 (11.6)
Cavernous sinus	16 (6.9)
Anterior clinoid process	14 (6)
Olfactory groove	14 (6)
Falx cerebri	7 (3)
Parasagittal region	7 (3)
Planum sphenoidale	7 (3)
Intraventricular	7 (3)
Optic nerve sheath	5 (2.1)
Posterior clinoid process	2 (0.9)
Infratentorial	**55 (23.6)**
Cerebellopontine angle	16 (6.9)
Petroclival region	10 (4.3)
Tentorium cerebella	9 (3.9)
Foramen magnum	8 (3.4)
Petrous bone	7 (3)
Clivus	3 (1.3)
Jugular foramen	2 (0.9)
Spinal	**12 (5.2)**
Thoracic spine	8 (3.4)
Cervical spine	3 (1.3)
Lumbar spine	1 (0.4)

Table 3. Tumor histopathology

Histopathology	Number (%)
WHO grade I	196 (84.1)
Meningothelial	119 (51.1)
Fibrous	22 (9.4)
Transitional	22 (9.4)
Psammomatous	8 (3.4)
Angiomatous	7 (3)
Secretory	7 (3)
Metaplastic	7 (3)
Lymphoplasmacyte-rich	4 (1.7)
WHO grade II	37 (15.9)
Brain-invasive	17 (7.3)
Atypical	14 (6)
Chordoid	3 (1.3)
Clear cell	3 (1.3)

Mean size of transitional meningiomas (3.2 cm) was significantly smaller than that of meningothelial (4.4 cm) and other (4.5 cm) subtypes ($p = 0.033$).

Meningiomas with hyposignal intensity on T2WI were more likely to be transitional and subtypes

Table 4. Correlation between clinical variables and WHO grades and subtypes of meningioma

Variables			WHO grades			Subtypes				
	n		I	II	*p*-value	Meningothelial	Fibrous	Transitional	Others	*p*-value
Age (year), mean ± SD	233		51.5±12.3	46.4±14.8	0.025*	50.3±12.9	55.0±11.6	53.7±11.5	50.7±13.2	0.182
Tumor size (cm), mean ± SD	233		4.1±1.8	5.1±1.5	0.005*	4.4±1.7	4.0±2.0	3.2±1.5	4.5±1.7	0.033*
Tumor location	233	Supratentorial	136	30	0.345	89	12	18	47	0.056
		Infratentorial	49	6		26	10	2	17	
		Spinal	11	1		4	0	2	6	
Calcification	184	Absent	121	23	0.547	71	14	13	46	0.708
		Present	32	8		17	4	6	13	
Cystic component	184	Absent	143	26	0.075	82	17	18	52	0.644
		Present	10	5		6	1	1	7	
En plaque appearance	184	Absent	131	29	0.232	71	18	17	54	0.074
		Present	22	2		17	0	2	5	
CSF cleft	184	Absent	42	13	0.108	26	4	3	22	0.278
		Present	111	18		62	14	16	37	
Vasogenic brain edema	184	Absent	71	4	0.001*	40	7	8	20	0.574
		Present	82	27		48	11	11	39	
Hyperostosis of the tumor base	184	Absent	66	10	0.262	35	10	7	24	0.624
		Present	87	21		53	8	12	35	
Bony destruction	184	Absent	149	29	0.273	85	18	18	57	0.863
		Present	4	2		3	0	1	2	
Tumor signal intensity on T1WI	140	Hyposignal	23	1	0.226	9	2	1	12	0.061
		Isosignal	77	15		47	13	11	21	
		Hypersignal	19	5		10	0	4	10	
Tumor signal intensity on T2WI	154	Hyposignal	8	2	0.011*	1	0	3	6	0.010*
		Isosignal	24	10		12	4	3	15	
		Hypersignal	100	10		60	13	12	25	
Tumor signal intensity on FLAIR	122	Hyposignal	6	2	<0.001*	1	0	3	4	0.065
		Isosignal	14	10		9	2	3	10	
		Hypersignal	82	8		46	12	8	24	
Tumor enhancement on CECT	91	Homogeneous	27	4	0.399	19	2	3	7	0.440
		Heterogeneous	48	12		30	4	3	23	
Tumor enhancement on T1WI	143	Homogeneous	37	10	0.119	20	2	7	18	0.223
		Heterogeneous	85	11		48	12	10	26	
Tumor consistency grading	233	I	42	5	0.372	26	10	0	11	0.005*
		II	108	20		67	5	15	41	
		III	46	12		26	7	7	18	

* Indicates statistically significant correlation ($p<0.05$). Data are presented as number or mean ± SD

other than meningothelial subtype. In contrast, hypersignal tumors on T2WI were more likely to be meningothelial subtype than other subtypes ($p = 0.010$).

Tumors with grade I consistency were significantly correlated with fibrous meningioma, rather than other subtypes. Grade II consistency meningiomas were more likely to be meningothelial, transitional, or subtypes other than fibrous variance ($p = 0.005$).

Regarding relationships between atypical features of meningioma and collected variables, the following associations were observed (Table 5):

Larger tumors were correlated with presence of small cell formation ($p<0.001$), necrosis ($p = 0.002$), and prominent nucleoli ($p = 0.006$).

Meningiomas with cystic component on neuroimaging were likely to exhibit small cell formation ($p = 0.004$), necrosis ($p = 0.031$), and prominent nucleoli ($p = 0.005$).

Tumors having peritumoral vasogenic edema were significantly associated with small cell formation ($p = 0.044$) and hypercellularity ($p = 0.003$).

Small cell formation and necrosis were correlated with tumors eliciting radiographic bony destruction ($p = 0.049$ and $p = 0.049$, respectively).

Meningiomas without necrosis were significantly correlated with tumors showing CSF cleft between tumor and brain on neuroimaging ($p = 0.023$).

Isosignal tumors in FLAIR imaging were likely to display small cell formation, necrosis, and hypercellularity, whereas hypersignal tumors were likely to be absent of those features ($p = 0.021$, $p = 0.043$, and $p<0.001$, respectively).

Isosignal tumors were likely to have hypercellularity on T2WI imaging, while hypersignal tumors were likely to have no hypercellularity ($p = 0.005$).

Tumors presenting homogeneous enhancement on T1WI imaging were likely to have small cell formation and hypercellularity. In contrast, meningiomas with heterogeneous enhancement were likely to be absent of both features ($p<0.001$ and $p<0.001$, respectively).

Regarding brain invasion, degree of connective tissue content, and calcification, we observed the following (Table 6):

Isosignal tumors on T2WI imaging were significantly likely to have brain invasion ($p = 0.043$). In addition, meningiomas showing isosignal intensity on FLAIR imaging were significantly correlated with brain invasion, whereas hypersignal intensity tumors were likely to have no brain invasion ($p = 0.017$).

Hyposignal tumors on FLAIR imaging were correlated with higher connective tissue content ($p = 0.004$).

Meningiomas with consistency grade I were more likely to have a low degree of connective tissue content ($p = 0.027$).

Mean age of patients with tumors absent microscopic calcification tended to be younger than patients with tumors showing microscopic calcification ($p = 0.004$).

Mean size of tumors without calcification in histopathology (4.5 cm) was significantly larger than that of tumors with high calcification (2.6 cm) ($p = 0.046$).

Meningiomas involving the spine were likely to have a high degree of calcification ($p<0.001$).

Presence of tumor calcification on neuroimaging was correlated with presence of calcification in histopathology ($p = 0.008$).

Hyposignal tumors on T2WI imaging were correlated with high degree of calcification in histopathology. Hypersignal tumors, in contrast, were likely to have either no calcification or low degree of calcification ($p<0.001$).

Isosignal tumors on FLAIR imaging were correlated with low degree of microscopic calcification, whereas hypersignal tumors were likely to have no calcification ($p<0.010$).

Discussion

Meningioma is a common neoplasm that develops in the neuraxis. Management of this tumor varies and is dependent upon several factors. WHO grade I tumors usually have a stable size or grow gradually over several years, whereas WHO grade II and III meningiomas have a higher risk of rapid growth. Differentiation between WHO grade I and high-grade meningiomas is useful for decision making in the management of these tumors. WHO grade I meningiomas found incidentally or with small-size can be treated by wait-and-see therapy or external beam radiation, but tumors with high-grade properties should be treated more aggressively.

Demographic characteristics

Meningiomas are 2 to 4 times more common in females than in males[7,8]. In our study, female to male tumor ratio was up to more than 5:1. WHO grades II and III are found in 21 to 37.8% of cases[5,9-11]. Zhou et al reported a proportion of WHO grade II meningioma

Table 5. Correlation between clinical variables and atypical histopathologic features

Variables			Small cell formation			Necrosis			Hypercellularity			Prominent nucleoli		
	n		Absent	Present	*p*-value	Absent	Present	*p*-value	Absent	Present	*p*-value	Absent	Present	*p*-value
Age (year), mean ± SD	233		50.2±11.7	52.9±17.1	0.221	51.0±12.6	49.6±13.8	0.526	50.4±13.0	52.6±11.9	0.378	50.9±12.6	47.4±17.5	0.376
Tumor size (cm), mean ± SD	233		4.0±1.7	5.2±1.8	<0.001*	4.1±1.6	5.1±2.0	0.002*	4.2±1.7	4.9±1.7	0.055	4.2±1.7	5.8±2.5	0.006*
Tumor location	233	Supratentorial	132	34	0.401	136	30	0.728	142	24	0.697	158	8	0.781
		Infratentorial	47	8		43	12		49	6		53	2	
		Spinal	11	1		9	3		11	1		11	1	
Calcification	184	Absent	120	24	0.122	118	26	0.526	128	16	0.140	136	8	0.428
		Present	29	11		31	9		32	8		39	1	
Cystic component	184	Absent	141	28	0.004*	140	29	0.031*	149	20	0.102	163	6	0.005*
		Present	8	7		9	6		11	4		12	3	
En plaque appearance	184	Absent	127	33	0.153	127	33	0.153	136	24	0.042	152	8	0.860
		Present	22	22		22	2		24	0		23	1	
CSF cleft	184	Absent	45	10	0.850	39	16	0.023*	48	7	0.934	51	4	0.328
		Present	104	25		110	19		112	17		124	5	
Vasogenic brain edema	184	Absent	66	9	0.044*	65	10	0.103	72	3	0.003*	72	3	0.642
		Present	83	26		84	25		88	21		103	6	
Hyperostosis of the tumor base	184	Absent	62	14	0.862	60	16	0.556	66	10	0.969	71	5	0.373
		Present	87	21		89	19		94	14		104	4	
Bony destruction	184	Absent	146	32	0.049*	146	32	0.049*	155	23	0.789	170	8	0.174
		Present	3	3		3	3		5	1		5	1	
Tumor signal intensity on T1WI	140	Hyposignal	19	5	0.516	21	3	0.537	23	1	0.233	23	1	0.418
		Isosignal	75	17		73	19		79	13		86	6	
		Hypersignal	17	7		18	6		19	5		24	0	
Tumor signal intensity on T2WI	154	Hyposignal	7	3	0.183	7	3	0.496	9	1	0.005*	9	1	0.268
		Isosignal	24	10		26	8		24	10		34	0	
		Hypersignal	92	18		91	19		101	9		103	7	
Tumor signal intensity on FLAIR	122	Hyposignal	6	2	0.021*	6	2	0.043*	8	0	<0.001*	7	1	0.320
		Isosignal	14	10		16	8		14	10		24	0	
		Hypersignal	76	14		79	11		82	8		84	6	
Tumor enhancement on CECT	91	Homogeneous	22	9	0.111	24	7	0.921	24	7	0.104	31	0	0.304
		Heterogeneous	51	9		47	13		54	6		58	2	
Tumor enhancement on T1WI	143	Homogeneous	30	17	<0.001*	36	11	0.334	32	15	<0.001*	44	3	0.774
		Heterogeneous	85	11		80	16		92	4		91	5	
Tumor consistency grading	233	I	39	8	0.896	39	8	0.331	44	3	0.292	43	4	0.265
		II	103	25		99	29		109	19		122	6	
		III	48	10		50	8		49	9		57	1	

* Indicates statistically significant correlation ($p<0.05$). Data are presented as number or mean ± SD

Table 6. Correlation between clinical variables and histopathologic analysis of brain invasion, degree of connective tissue content, and calcification

Variables	n		Brain Invasion			Degree of connective tissue content				Degree of microscopic calcification			
			Absent	Present	*p*-value	Low	Moderate	High	*p*-value	Absent	Low	High	*p*-value
Age (yr), mean ± SD	233		50.7±13.1	49.2±10.3	0.582	52.1±12.9	47.8±11.7	50.4±14.3	0.078	47.6±11.8	51.9±13.2	60.5±8.6	0.004*
Tumor size (cm), mean ± SD	233		4.2±1.8	4.5±0.7	0.663	4.4±1.9	4.0±1.5	4.2±1.6	0.364	4.5±1.9	4.3±1.7	2.6±1.2	0.046*
Tumor location	233	Supratentorial	149	17	0.171	108	40	18	0.064	63	102	1	<0.001*
		Infratentorial	53	2		25	21	9		13	39	3	
		Spinal	12	0		7	5	0		4	4	4	
Calcification	184	Absent	133	11	0.977	86	42	16	0.958	51	90	3	0.008*
		Present	37	3		23	12	5		5	32	3	
Cystic component	184	Absent	156	13	0.886	101	50	18	0.551	52	111	6	0.694
		Present	14	1		8	4	3		4	11	0	
En plaque appearance	184	Absent	147	13	0.495	99	45	16	0.122	47	107	6	0.493
		Present	23	1		10	9	5		9	15	0	
CSF cleft	184	Absent	50	5	0.620	33	16	6	0.987	19	34	2	0.702
		Present	120	9		76	38	15		37	88	4	
Vasogenic brain edema	184	Absent	75	0	0.001	40	25	10	0.399	27	45	3	0.323
		Present	95	14		69	29	11		29	77	3	
Hyperostosis of the tumor base	184	Absent	73	3	0.116	43	25	8	0.671	23	49	4	0.436
		Present	97	11		66	29	13		33	73	2	
Bony destruction	184	Absent	165	13	0.395	105	52	21	0.671	54	118	6	0.896
		Present	5	1		4	2	0		2	4	0	
Tumor signal intensity on T1WI	140	Hyposignal	23	1	0.760	14	5	5	0.302	9	13	2	0.090
		Isosignal	84	8		52	32	8		22	69	1	
		Hypersignal	22	2		16	5	3		4	18	2	
Tumor signal intensity on T2WI	154	Hyposignal	10	0	0.043*	4	3	3	0.186	1	6	3	<0.001*
		Isosignal	28	6		24	8	2		6	26	2	
		Hypersignal	104	6		61	36	13		32	77	1	
Tumor signal intensity on FLAIR	122	Hyposignal	7	1	0.017*	2	2	4	0.004*	1	6	1	0.010*
		Isosignal	18	6		17	7	0		1	23	0	
		Hypersignal	85	5		53	27	10		30	58	2	
Tumor enhancement on CECT	91	Homogeneous	30	1	0.352	14	13	4	0.140	6	25	0	0.079
		Heterogeneous	55	5		40	15	5		22	35	3	
Tumor enhancement on T1WI	143	Homogeneous	43	4	0.971	28	15	4	0.757	9	34	4	0.126
		Heterogeneous	88	8		53	31	12		27	67	2	
Tumor consistency grading	233	I	44	3	0.450	36	7	4	0.027*	19	27	1	0.393
		II	119	9		76	40	12		47	76	5	
		III	51	7		28	19	11		14	42	2	

* Indicates statistically significant correlation ($p<0.05$); Data are presented as number or mean ± SD. Degree of connective tissue content: low (<30% per HPF); moderate (30-60% of HPF); and, high (>60% of HPF). Degree of microscopic calcification: absent (0% per HPF); low (<50% of HPF); and, high (>50% of HPF)

of 21.3%[8]. In the present study, we found WHO grade II meningioma in 15.9% of patients. This proportion is slightly less than any grade II proportion ever reported.

Prediction of WHO grades of meningioma

Previous studies showed that male, younger age, larger tumor size, irregular shape, lateral and non-skull base locations, and peritumoral vasogenic edema correlated with high-grade (WHO grades II to III) meningioma[8,12,13]. Because our series had no cases with WHO grade III, we conclude that younger age, larger tumor size, peritumoral vasogenic edema, and tumors demonstrating isosignal intensity on T2WI and FLAIR imaging can be used to predict a possibility of WHO grade II meningioma.

Prediction of histopathologic subtypes of meningioma

In the present study, hyposignal tumors on T2WI imaging were likely to be transitional subtype, whereas meningothelial meningiomas were associated with hypersignal intensity. These correlations were identical to those of previous studies[14-17]. In studies conducted prior to the implementation of WHO 2007 classification of central nervous system tumors, some studies found tumors exhibiting hard consistency to be directly correlated with fibroblastic subtype[18,19]. In addition to focusing on tumor component, we also focused on connective tissue component. To our knowledge, no previous studies have investigated correlation between tumor consistency and amount of connective tissue. From our findings, tumors with soft consistency were likely to be fibrous subtype, whereas firmer tumors were likely to be meningothelial, transitional, or other variations. Moreover, soft consistency tumors were likely to have a lower amount of connective tissue component. Subgroup analysis showed that meningioma subtypes and amount of connective tissue were not confounding factors. We, therefore, believe that meningioma consistency is constituted from both components. Furthermore, our study showed that hyposignal meningiomas on FLAIR imaging contained a higher amount of connective tissue component. This finding, according to our review of previous studies, has not been mentioned in any previous reports.

Prediction of atypical features and meningioma with brain invasion

Based on our review of the literature, no prior study has investigated direct correlation between clinical parameters and atypical features of meningioma, which are the criteria for diagnosis of high-grade meningioma. From our findings, we can conclude that presence of cystic component, peritumoral vasogenic edema, bony erosion on neuroimaging, isosignal intensity of tumor on T2WI and FLAIR imaging, and homogeneous enhancement of tumor on T1WI can be used as predictors of an individual atypical feature. We also found that absence of CFS cleft between the tumor and brain can reliably predict necrosis. Brain invasion is a unique criterion for diagnosing WHO grade II meningioma. Importantly, we found that isosignal intensity tumor on T2WI and FLAIR imaging can also predict this feature.

Predictors correlating with microscopic calcification

Calcification visualized on neuroimaging was found to be directly concordant with microscopic calcification. Hyposignal tumors on T2WI imaging had more microscopic calcification. On the contrary, meningiomas with hypersignal intensity on T2WI and FLAIR imaging had less calcification in histopathology. Meningiomas situated in the supratentorial and spinal regions tended to have microscopic calcification. Based on our review of the literature, this is the first study to report this finding.

Conclusion

Younger age, peritumoral brain edema, and isosignal intensity tumors on T2W and FLAIR imaging can be utilized for predicting the possibility of WHO grade II meningioma. Existence of cystic component, peritumoral brain edema, and bony erosion in pre-operative neuroimaging can be independently used to forecast occurrence of some atypical histopathological features. Meningiomas showing hyposignal intensity on T2WI tend to be transitional subtype, whereas hypersignal tumors portend meningothelial variance. Intra-operative soft consistency can be used to predict the possibility of fibrous subtype, and is associated with a low level of connective tissue in histopathology.

What is already known from this topic?

Several factors, including male, younger age, larger tumor size, irregular shape, lateral and non-skull base locations, and peritumoral vasogenic edema, are associated with high-grade (WHO grades II to III) meningiomas. Meningiomas with hard consistency tend to be fibroblastic subtype. To date, no previous

study has investigated correlation between tumor consistency and amount of connective tissue, correlation between clinical parameters and atypical histopathological features, and predictors of microscopic calcification.

What this study adds?

Factors correlated with a possibility of WHO grade II meningioma are young age, larger tumor size, peritumoral edema and isosignal intensity of tumor on T2WI and FLAIR image. Hyposignal tumors on T2WI are associated with transitional meningioma, whereas hypersignal tumors on T2WI are correlated with meningothelial subtypes. Meningiomas with soft consistency tend to be fibrous subtype and tend to contain a low level of connective tissue. Radiographic predictors of atypical histopathologic features are presence of cystic component, peritumoral edema, bony erosion and absence of CFS cleft between tumor and brain, and homogeneous enhancement of tumor on T1WI. Radiographic predictors of atypical features include presence of cystic component, peritumoral edema, bony erosion and absence of CFS cleft between tumor and brain, and homogeneous enhancement of tumor on T1WI. Tumor isosignal intensity on T2WI and FLAIR image can predict appearance of atypical features and brain invasion in histopathology. Small size, spinal location, and hyposignal intensity of tumors on T2WI were correlated with dense microscopic calcification.

Potential conflicts of interest

None.

References

1. Longstreth WT Jr, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD. Epidemiology of intracranial meningioma. Cancer 1993; 72: 639-48.
2. Louis DN, Ogaki K, Wiestler OD, Cavanee WK, editors. World Health Organization classification of tumours of the central nervous system. Lyon, Franc: IARC Press; 2007.
3. Walcott BP, Nahed BV, Brastianos PK, Loeffler JS. Radiation Treatment for WHO grade II and III meningiomas. Front Oncol 2013; 3: 227.
4. Ding D, Starke RM, Hantzmon J, Yen CP, Williams BJ, Sheehan JP. The role of radiosurgery in the management of WHO grade II and III intracranial meningiomas. Neurosurg Focus 2013; 35: E16.
5. Modha A, Gutin PH. Diagnosis and treatment of atypical and anaplastic meningiomas: a review. Neurosurgery 2005; 57: 538-50.
6. Sitthinamsuwan B, Khampalikit I, Nunta-aree S, Srirabheebhat P, Witthiwej T, Nitising A. Predictors of meningioma consistency: A study in 243 consecutive cases. Acta Neurochir (Wien) 2012; 154: 1383-9.
7. Oya S, Kim SH, Sade B, Lee JH. The natural history of intracranial meningiomas. J Neurosurg 2011; 114: 1250-6.
8. Zhou P, Ma W, Yin S, Li Y, Jiang S. Three risk factors for WHO grade II and III meningiomas: A study of 1737 cases from a single center. Neurol India 2013; 61: 40-4.
9. Sade B, Chahlavi A, Krishnaney A, Nagel S, Choi E, Lee JH. World Health Organization grades II and III meningiomas are rare in the cranial base and spine. Neurosurgery 2007; 61: 1194-8.
10. Rogers L, Gilbert M, Vogelbaum MA. Intracranial meningiomas of atypical (WHO grade II) histology. J Neurooncol 2010; 99: 393-405.
11. Aghi MK, Carter BS, Cosgrove GR, Ojemann RG, Amin-Hanjani S, Martuza RL, et al. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. Neurosurgery 2009; 64: 56-60.
12. Mattei TA, Mattei JA, Ramina R, Aguiar PH, Plese JP, Marino JR. Edema and malignancy in meningiomas. Clinics (Sao Paulo) 2005; 60: 201-6.
13. Chernov MF, Kasuya H, Nakaya K, Kato K, Ono Y, Yoshida S, et al. ^{1}H-MRS of intracranial meningiomas: what it can add to known clinical and MRI predictors of the histopathological and biological characteristics of the tumor? Clin Neurol Neurosurg 2011; 113: 202-12.
14. Englund E, Brun A, Larsson EM, Gyorffy-Wagner Z, Persson B. Tumours of the central nervous system. Proton magnetic resonance relaxation times T1 and T2 and histopathologic correlates. Acta Radiol Diagn (Stockh) 1986; 27: 653-9.
15. Soyama N, Kuratsu J, Ushio Y. Correlation between magnetic resonance images and histology in meningiomas: T2-weighted images indicate collagen contents in tissues. Neurol Med Chir (Tokyo) 1995; 35: 438-41.
16. Maiuri F, Iaconetta G, de Divitiis O, Cirillo S, Di Salle F, De Caro ML. Intracranial meningiomas: correlations between MR imaging and histology. Eur J Radiol 1999; 31: 69-75.
17. Kaplan RD, Coons S, Drayer BP, Bird CR, Johnson PC. MR characteristics of meningioma subtypes at 1.5 tesla. J Comput Assist Tomogr

1992; 16: 366-71.
18. Suzuki Y, Sugimoto T, Shibuya M, Sugita K, Patel SJ. Meningiomas: correlation between MRI characteristics and operative findings including consistency. Acta Neurochir (Wien) 1994; 129: 39-46.
19. Carpeggiani P, Crisi G, Trevisan C. MRI of intracranial meningiomas: correlations with histology and physical consistency. Neuroradiology 1993; 35: 532-6.

ตัวพยากรณ์ทางคลินิกของระดับเนื้องอกตามการแบ่งขององค์การอนามัยโลก, ชนิดย่อยและลักษณะทางพยาธิวิทยาที่ผิดปกติของ meningioma

อินธิรา ขัมภลิขิต, พรสุข ชื่นสุชน, บรรพต สิทธินามสุวรรณ

ภูมิหลัง: *meningioma ระดับหนึ่งตามการแบ่งขององค์การอนามัยโลกมีการดำเนินโรคแบบค่อยเป็นค่อยไปในขณะที่ meningioma ระดับสองและสามมีการดำเนินโรคที่รุนแรงมากกว่า*

วัตถุประสงค์: *เพื่อศึกษาตัวพยากรณ์ทางคลินิกของระดับเนื้องอกตามการแบ่งขององค์การอนามัยโลก, ชนิดย่อยและลักษณะทางพยาธิวิทยาที่ผิดปกติของ meningioma*

วัสดุและวิธีการ: *ทำการวิเคราะห์ความสัมพันธ์ระหว่างตัวแปรทางคลินิกกับระดับเนื้องอกตามการแบ่งขององค์การอนามัยโลก, ชนิดย่อย, ลักษณะทางพยาธิวิทยาที่ผิดปกติ, ลักษณะที่เนื้องอกลามเข้าเนื้อสมอง, ปริมาณเนื้อเยื่อเกี่ยวพันและการมีแคลเซียมในเนื้องอก*

ผลการศึกษา: *จาก meningioma 233 ราย 196 ราย (ร้อยละ 84.1) เป็นระดับหนึ่งและ 37 ราย (ร้อยละ 15.9) เป็นเนื้องอกระดับสอง ไม่มีเนื้องอกระดับสามในงานวิจัยนี้ ปัจจัยที่มีความสัมพันธ์กับความเป็นไปได้ที่จะเป็น meningioma ระดับสอง ได้แก่ อายุน้อย (p = 0.025) เนื้องอกขนาดใหญ่ (p = 0.005) ภาวะสมองบวมรอบเนื้องอก (p = 0..001) และ meningioma ที่มีความเข้มเท่ากับเนื้อสมองในการตรวจภาพแม่เหล็กไฟฟ้าของสมองชนิด T2W (p = 0.011) และ FLAIR (p<0.001) meningioma ที่มีความเข้มต่ำกว่าเนื้อสมองในการตรวจภาพแม่เหล็กไฟฟ้าของสมองชนิด T2W สัมพันธ์กับชนิดย่อย transitional และ meningioma ที่มีความเข้มสูงกว่าเนื้อสมองในการตรวจภาพแม่เหล็กไฟฟ้าของสมองชนิด T2W สัมพันธ์กับชนิดย่อย meningothelial นอกจากนี้ยังพบว่า meningioma ที่นุ่มมีแนวโน้มที่จะเป็นชนิดย่อย fibrous ซึ่งสัมพันธ์กับปริมาณเนื้อเยื่อเกี่ยวพันในเนื้องอกที่มีปริมาณต่ำ ตัวบ่งชี้ทางรังสีวิทยาของลักษณะที่ผิดปกติของ meningioma ได้แก่ การพบส่วนที่เป็นถุงน้ำในเนื้องอก ภาวะสมองบวมรอบเนื้องอก พบการทำลายของกระดูกที่อยู่ใกล้เนื้องอก ไม่พบช่องน้ำหล่อสมองและไขสันหลังระหว่างเนื้องอกกับสมองและเนื้องอกเป็นสีขาวเหมือนกันทั้งก้อนในการตรวจภาพแม่เหล็กไฟฟ้าของสมองชนิด T1W ร่วมกับการฉีดสารทึบรังสี meningioma ที่มีความเข้มเท่ากับเนื้อสมองในการตรวจภาพแม่เหล็กไฟฟ้าของสมองชนิด T2W และ FLAIR มีความสัมพันธ์กับลักษณะผิดปกติของเนื้องอกและลักษณะที่เนื้องอกลามเข้าเนื้อสมองในการตรวจทางพยาธิวิทยา เนื้องอกที่มีขนาดเล็กอยู่บริเวณช่องกระดูกสันหลังและมีความเข้มของเนื้องอกต่ำกว่าเนื้อสมอง ในการตรวจภาพแม่เหล็กไฟฟ้าของสมองชนิด T2W สัมพันธ์กับการพบแคลเซียมปริมาณมากในเนื้องอก*

สรุป: *สามารถใช้ปัจจัยทางคลินิกหลายอย่างเพื่อช่วยในการพยากรณ์ความเป็นไปได้ที่จะเป็น meningioma ระดับสองและสาม ชนิดย่อยและลักษณะผิดปกติของเนื้องอก ซึ่งข้อมูลเหล่านี้มีประโยชน์ในแง่การรักษาเนื้องอก*