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Histopathological Spectrum of Meningiomas with Emphasis on Prognostic Role of Ki67 Labelling Index

Girish Solanke[1], Vidya Monappa*[1], Ranjini Kudva[1]

1. *Department of Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India-576104*

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ABSTRACT

Background & Objective: Meningiomas are the most frequently encountered primary non-glial tumors of the central nervous system (CNS). The Ki67 labelling index (Ki67LI) is a proliferation marker that may prove useful in determining the histological grade. This study aims at: 1) Studying the frequency, grade and histomorphological spectrum of meningiomas, 2) Evaluating 20 histological parameters and determining its utility in grading meningiomas and 3) Comparing the Ki67LI in the various subtypes and WHO grades.

Methods: The cases of meningiomas diagnosed in our Department from June 2009 to May 2014 were included. The clinical details, grade and 20 histological parameters: mitosis, vesicular nuclei, macronucleoli, nuclear pleomorphism, scattered bizarre nuclei, hypercellularity, sheeting, lymphocytes, small cell change, foam cells, ossification, necrosis, papillary change, lipidization, psammoma bodies, vascularization, brain invasion, dural invasion, bone invasion and other soft tissue invasion were recorded for each case. The average and highest Ki67LI was recorded as percentage and number per high power field.

Results: A total of 175 cases of meningioma were included: grade I (145), grade II (30). Atypical histological features like hypercellularity, sheeting, etc. were common in grade II tumors. Increased vascularity, lymphocytes and psammoma bodies were common in grade I tumors. Ki67LI (highest) ranged from 1-6% in grade I and 5-12% in grade II tumors.

Conclusion: Among different methods showing mitotic activity, Ki67% (highest) was the most statistically significant LI in differentiating grade I and grade II tumors. The median Ki67% (highest) was 4% for grade I and 7% for grade II tumors.

Corresponding Information: **Vidya Monappa**; Department of Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India-576104 Email: vidsdr@yahoo.co.in

Introduction

Meningiomas are neoplasms that are derived from the arachnoid cap (meningothelial cells) of the brain and spinal cord meningeal coverings. They are the most common primary tumors of the central nervous system accounting for 20-36% of the cases (1,2). They are seen mostly in middle-aged to elderly adults with peak incidence in the 6th to 7th decades of life. They are more common in women with a female:male ratio of nearly 2:1 (3). They are generally benign, slow growing tumors that produce neurological symptoms related to the compression of adjacent structures.

Meningiomas can occur all along the craniospinal axis. In the cranial cavity, meningiomas occur most frequently along the cerebral convexity, olfactory groove and sphenoid ridges. Less common sites include intraventricular and epidural region. Atypical and anaplastic meningiomas occur in non-skull-base sites (2).

Morphologically, meningiomas are heterogenous and several histological types of them have been described. Of more clinical significance is the histological grade which corresponds to the benign/aggressive nature of the tumor. Atypical meningioma is an intermediate grade tumor between benign and malignant forms. Its diagnosis is based on increased mitotic activity, brain invasion or at least 3 of the 5 histologic features (increased cellularity, small cell change, sheeting, prominent nucleoli and foci of spontaneous necrosis) (1). The 5 histologic features however lack precise definition and thus account for the interpretation bias. However, in the absence of other histomorphologic features, their recognition plays a major role in accurate grading of meningiomas. Also, some of these features may be seen in grade 1 tumors adding to the diagnostic confusion. Ki67 index

can prove useful in this regard, however, literature does not define the Ki67LI cut-off range for grading meningiomas.

This study was designed 1) To study the histopathological spectrum and frequency of occurrence of meningiomas in accordance with the 2016 WHO classification; 2) To evaluate the various histological parameters used in the grading of meningiomas; and 3) To compare the Ki67 labelling index (Ki67LI) among the various histological subtypes.

Materials and Methods

This is a retrospective study. All cases of meningiomas diagnosed in the Department of Pathology, at our Institute over a five-year period from June 2009 to May 2014 were included in this study. The medical records of the patients were reviewed and details of age, gender, clinical presentation, radiological features, location and recurrence if any were noted.

The histological sections stained by haematoxylin and eosin (H&E) were reviewed. All tumors were graded according to WHO 2016 criteria. For each case, 20 histological parameters were recorded: mitosis, vesicular nuclei, prominent (macro) nucleoli, nuclear pleomorphism, scattered bizarre nuclei, hyper cellularity, sheeting or pattern-less growth, lymphocytes, small cell change, foam cells, ossification, necrosis, papillary change, lipidization, psammoma bodies, vascularization, brain invasion, dural invasion, bone invasion and other soft tissue invasion. Mitosis was recorded as no./10 high power field (hpf) in the area with the highest proliferative activity.

Psammoma bodies were assessed semi-quantitatively as absent, + (occasional), ++ (<50%) and +++ (>50%) tumor volume. Lymphocytes were also assessed semi-quantitatively as absent, + (few), ++ (moderate) and +++ (dense) infiltration. Vascularization was assessed semi-quantitatively as absent, + (occasional), ++ (frequent) and +++ (numerous) blood vessels. All the other parameters were recorded as present or absent.

Macronucleoli was considered as present when it was observable under 10x objective. Hypercellularity was considered present when >53 nuclei/hpf were seen. Sheeting was defined as loss of whorled or fascicular growth patterns. Small cell change was considered when tumor cells showed increased nuclear to cytoplasmic ratio (lymphocyte-like morphology). Brain invasion was defined as irregular tongue-like protrusions of tumor cells into adjacent brain parenchyma without a layer of leptomeninges.

Immunohistochemistry using MIB-1 antibody; ready to use monoclonal mouse antibody provided in liquid form in a buffer containing stabilizing protein and 0.015 mol/L sodium azide. Clone: MIB-1. Isotype: IgG1, kappa, DAKO, Denmark was performed on 70 cases (41 grade I and 29 grade II meningiomas). The Ki67 labelling index (LI) was expressed in 2 ways: 1) percentage, i.e. number of positive cells in 100 tumor cells, 2) number of positive tumor cells per hpf. The Ki67 counting was performed in 2 ways: 1) taking average count including all areas, 2) taking the highest count in the areas with the greatest degree of immunostaining.

Additional immunohistochemical markers like epithelial membrane antigen (EMA), Cytokeratin (CK), Vimentin, Glial fibrillary acidic protein (GFAP), etc. were performed whenever necessary to facilitate the diagnosis.

The statistical analysis was done using Chi-square/ Fisher exact test and P-value of less than 0.05 was considered as significant.

Results

A total of 175 cases of meningiomas were included in this study. Exclusion criteria were missing slides and blocks.

Of these, 154 cases (88%) were intracranial, 20 cases (11.42%) were in the spinal region and 1 case (0.57%) was extra cranial in location, situated in the parotid region. The cerebral convexity represented the single most common site of tumor occurrence. In the spinal location, thoracic region was the most commonly affected area, followed by cervical and lumbar region. In one case, both thoracic and lumbar regions (D12-L3) were involved.

The age at the time of initial diagnosis ranged from 15-78 years with the mean age of 48.46 years (± 13.28). Most of the cases were in the 4^{th} to 7^{th} decades, while 5^{th} and 6^{th} decades accounted for 50.3% of the cases. There was gender predominance with 117 females and 58 males. The overall female to male ratio was 2.01:1. In the spinal location, female to male ratio was 9:1.

The common clinical presentations were headache, vomiting, seizures, weakness of limbs, visual symptoms, smell disturbance and gait disturbances.

The radiological features like bone erosion and peritumoral edema were more commonly seen in grade II meningiomas (13.3% & 20%, respectively) when compared to the grade I meningiomas (4.8% & 11.03%, respectively). However, calcification was seen more commonly in grade I (9.6%) than grade II (6.6%) meningiomas. Tumor size ranged from 0.46-8 cm with a mean of 4.22 cm (± 1.64). The larger size tumors were generally of higher grade.

In accordance with 2016 WHO classification 145 cases (82.9%) were classified as grade I and 30 cases (17.1%) as grade II. There was no case of grade III meningioma. The distribution of the histologic subtypes of meningiomas is as depicted in Table 1 and the histopathology images are shown in Figure 1.

The frequency and percentage of the 20 histopathological features in grades I vs II of meningiomas and the statistical association between these features in the two grades are depicted in Table 2.

The histopathological features useful in diagnosing grade II meningiomas are as shown in Figure 2.

The features like scattered bizarre cells, necrosis, sheeting, macronucleoli, nuclear pleomorphism, small cell change and papillary change occurred more frequently in grade II (P<0.05). Among the 30 grade II cases, psammoma bodies were absent in 19 cases.

Numerous blood vessels (+++) was seen in grade I meningiomas but not in grade II meningiomas. This can be explained by the proliferation of blood vessels seen in angiomatous and to a lesser extent in microcystic meningiomas. Vascularity was least in psammomatous and fibroblastic meningiomas. Lymphoplasmacyte-rich meningioma showed dense infiltrate of lymphocytes (+++) along with plasma cells almost obscuring the meningothelial cells. Hypercellularity and sheeting were also seen in grade I (meningothelial and transitional) meningiomas. Nuclear pleomorphism was observed in 50% of angiomatous and 80% of microcystic meningiomas.

Clear cell and chordoid variants (20%) were diagnosed solely based on the distinct histomorphology. Brain invasion (BI), increased mitosis (Mi) and atypical features (AF) were observed in 40%, 43.33% and 46.66% of grade II meningiomas, respectively. The presence of only one histologic feature (BI, Mi, AF) contributed to the diagnosis in a smaller percentage of cases (25%, 14.2, 14.2%, respectively). All 3 features were noted in only 3 cases (12.5%)

There were 15 cases of recurrent meningiomas in this study. The age range of recurrent meningiomas was 26-76 years. It was more common in the 5th decade (33.3% of recurrent cases) with a female to male ratio was 1.5:1. Out of the 15 recurrent meningiomas, 5 cases were WHO grade II.

Table 1. Histologic subtypes of meningiomas seen in this study

WHO Grade I (82.90%, N = 145)		
Histological subtype	N	%
Meningothelial	43	24.6
Transitional	42	24
Fibroblastic	23	13.1
Psammomatous	11	6.3
Angiomatous	10	5.7
Microcystic	10	5.7
Sclerotic	2	1.1
Lymphoplasmacyte rich	2	1.1
Metaplastic	1	0.6
Secretory	1	0.6
WHO Grade II (17.10%, N = 30)		
Histological subtype	N	%
Atypical	24	13.7
Clear cell	3	1.7
Chordoid	3	1.7

Table 2. The histopathological features in relation to WHO grade and associations between grade I and II (Chi-square or Fisher exact test).

Histological Characteristics	**Recorded as**	**Total cases (n=175)**		**WHO grade I (n=145)**		**WHO grade II (n=30)**		**P-value WHO I vs II**
		Frequency	**Percent**	**Frequency**	**Percent**	**Frequency**	**Percent**	
Scattered bizarre cells	Present/absent	23	13	15	10.3	8	26.7	0.032
Ossification	Present/absent	3	1.7	3	2.1	0	0	1.000
Necrosis	Present/absent	10	5.7	4	2.8	6	20	0.002
Foam cells	Present/absent	16	9	12	8.3	4	13.3	0.483
Sheeting	Present/absent	46	26.3	28	19.3	18	60	0.000
Macronucleoli	Present/absent	23	13.1	14	9.7	9	30	0.006
Nuclear pleomorphism	Present/absent	49	28	34	23.4	15	50	0.004
Vesicular nuclei	Present/absent	9	5	8	5.5	1	3.3	1.000

Histological Characteristics	Recorded as	Total cases (n=175)		WHO grade I (n=145)		WHO grade II (n=30)		P-value WHO I vs II
		Frequency	Percent	Frequency	Percent	Frequency	Percent	
Hypercellularity	Present/absent	45	25.7	32	22.1	13	43.3	0.021
Small cell change	Present/absent	21	12	8	5.5	13	43.3	0.000
Lipidization	Present/absent	4	2.3	3	2.1	1	3.3	0.532
Papillary change	Present/absent	5	2.9	2	1.4	3	10	0.036
Microcystic change	Present/absent	28	16	24	16.6	4	13.3	0.790
Dural infiltration	Present/absent	25	14.3	19	13.1	6	20	0.388
Bone infiltration	Present/absent	11	6.3	8	5.5	3	10	0.404
Other soft tissue infiltration	Present/absent	5	2.9	4	2.8	1	3.3	1.000
Increased vascularity	Absent	71	40.5	64	44.1	7	23.3	
	+	55	31.4	46	31.7	9	30	
	++	34	19.4	20	13.8	14	46.6	
	+++	15	8.6	15	10.3	0	0	
Lymphocytes	Rare	79	45.1	60	41.4	19	63.3	
	+	68	38.9	60	41.4	8	26.7	
	++	26	14.9	23	15.9	3	10	
	+++	2	1.1	2	1.4	0	0	
Psammoma bodies	Absent	59	33.7	40	27.6	19	63.3	
	+	61	34.9	54	37.2	7	23.3	
	++	44	25.1	40	27.6	4	13.3	
	+++	11	6.2	11	7.5	0	0	

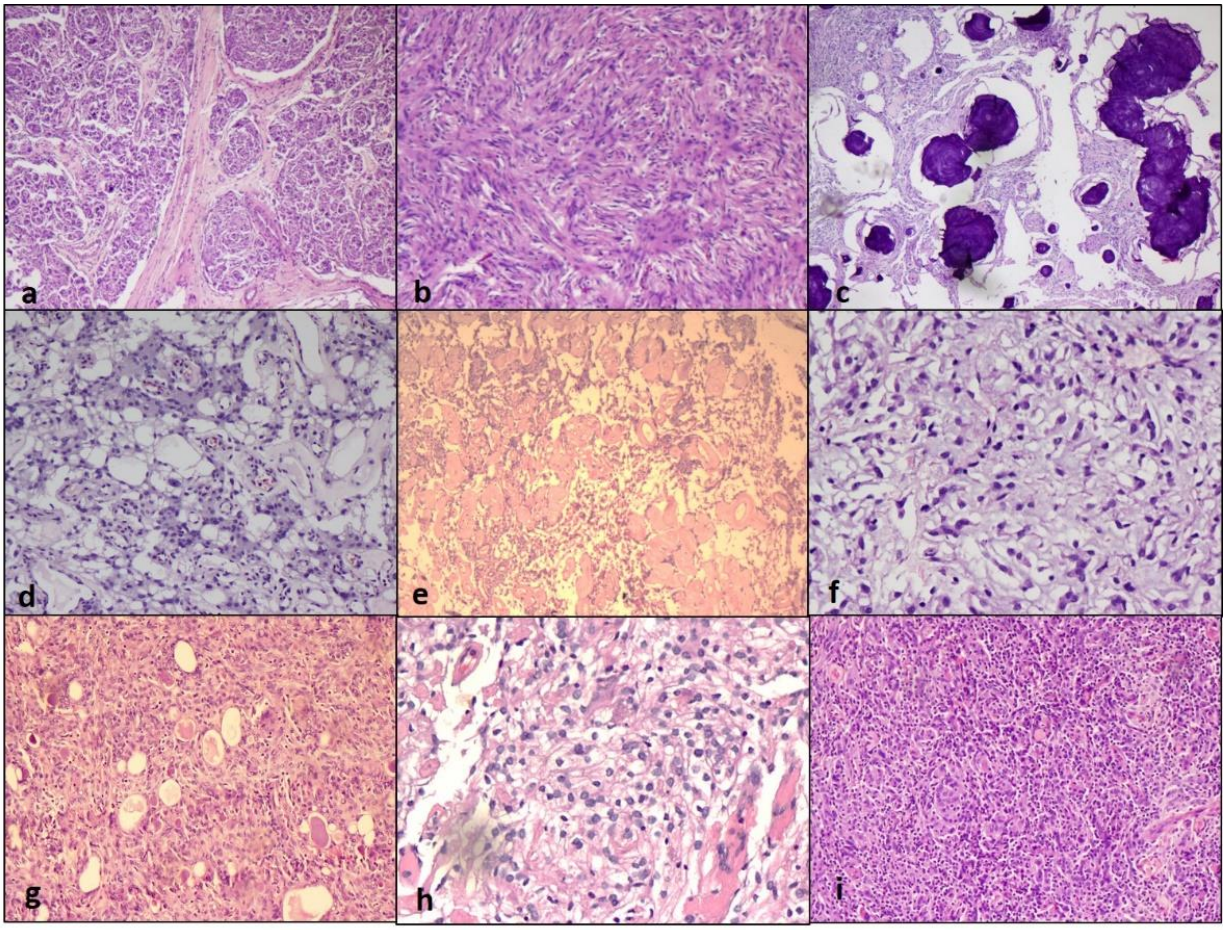

Fig. 1. H&E staining of meningioma: a) Meningothelial variant, whorls, 200X; b) Fibroblastic variant, 200X; c) Psammomatous variant, 200X; d) Microcystic variant, 200X; e) Angiomatous variant, 200X; f) Chordoid variant, 400X; g) Secretory variant, 200X; h) Clear cell variant, 400X; i) Lymphoplasmacyte rich variant, 200X

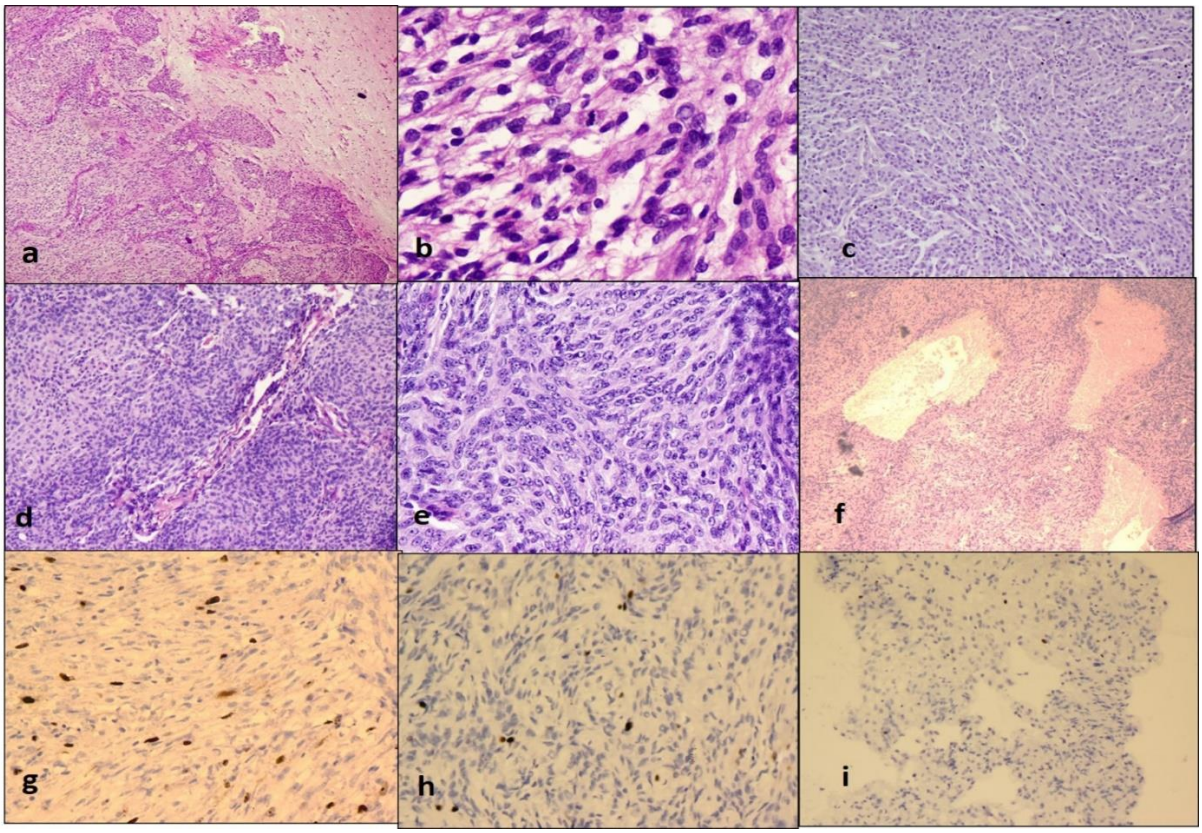

Fig. 2. Atypical features, H&E: a) Brain invasion, 200X; b) Mitosis, 400X; c) Increased cellularity and sheeting, 200X; d) Small cell change, 200X; e) Prominent nucleoli, 400X; f) Necrosis, 100X; Ki67 IHC: g) High – 10%, 400X; h) Low- 2%, 400X; i) Low- <1%, 200X

KI67 LI

Ki67 or MIB-1 immunohistochemical stain was performed on 70 cases which included 41 grade I cases and 29 grade II cases. Ki67 LI using counts per hpf were higher (>15/hpf) for meningothelial, transitional and angiomatous variants bordering on the counts found in atypical meningiomas; Ki67% was lower. As the number of recurrent tumors was less (3), they were not included for statistical analysis, however, the Ki67LI was observed to be higher at the time of tumor recurrence (Ki67% average: 3,2,6 vs 1,4,15, respectively) (Ki67% highest: 5,5,12 vs 2,6,24, respectively).

Table 3 depicts the median with interquartile range of Ki67% and Ki67 per hpf in grade I and grade II meningiomas.

Table 3. Ki-67% and Ki-67/hpf in WHO grade I and II

	Ki-67 % (Average)	Ki-67 % (Highest)	Ki-67/hpf (Average)	Ki-67/hpf (Highest)
WHO grade I (n=41)	2 (1, 3)	4 (2, 5)	5 (2, 11)	12 (6, 25)
WHO grade II (n=29)	3 (2, 5.5)	7 (4.5, 10.5)	12 (7, 19)	25 (15, 41)
P value Grade I vs. II	0.003	0.000	0.004	0.032

n = number of cases in which Ki-67 was done, above values show median with interquartile range

Discussion

The WHO classifications of meningiomas were published in the years 1979, 1993 and 2000, to introduce more objective and reproducible diagnostic criteria. The 2007 (and older version; 2000) classification scheme of WHO is based on the 2 studies done in Mayo Clinic (4,5). The only difference between WHO 2007 & 2016 classifications in comparison with the 2000 edition is that otherwise benign meningiomas with brain invasion are classified as grade II as they have a higher chance of recurrence.

The WHO 2016 classification has put forward several diagnostic criteria for grading of meningiomas,

however, there is no clear guidelines regarding Ki67 proliferation index: Grade I: Mitosis of up to 4/10 high power (40X magnification, 0.16 mm^2) field and includes Fibrous, transitional, meningothelial, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte rich and metaplastic variants; Grade II: 1. Increased mitosis of >4/10 high power (40X magnification, 0.16 mm^2) fields, 2. Brain invasion, 3. At least 3 features: increased cellularity, small cell change, sheeting, high N:C ratio, prominent nucleoli, spontaneous necrosis. Atypical chordoid and clear cell meningioma are by default placed in grade II; and Grade III: Mitotic count of >20/10 high power (40X magnification, 0.16mm^2) field, Ki67 >20% which include anaplastic, rhabdoid and papillary variants.

Categorizing these tumors into histological subtypes is generally of little significance in grade I meningiomas. However, recognition of special variants and atypical meningiomas is of paramount importance due to their more aggressive and recurrent nature. We had 3 cases each of clear cell and chordoid meningiomas. Both variants were diagnosed as grade II based on the characteristic histomorphology. None of the tumors showed brain invasion, however, Ki67LI was high (>6%) in 4 of the 6 cases. The frequency of diagnosis of atypical meningiomas was however, less in our study (13.7%) in comparison with the other authors (Grondahl *et al.* 29.1% (6), Babu *et al.* 23.3% (7)). Lack of clear morphological description of the 6 atypical features may have resulted in under diagnosis of a few potentially grade II meningiomas.

Some of the 5 atypical histological features are not clearly described in literature. Prominent nucleoli should be considered only under 10X magnification (3). History of embolization and radiation should be ruled out before reporting necrosis. WHO strictly states that only spontaneous necrosis should be considered (8). Sheeting is defined as uninterrupted pattern less or sheet like growth (loss of whorled or fascicular growth pattern) (8). This definition is not much specific because, meningothelial meningioma grows in syncytial sheets and it may simulate sheeting pattern. Hypercellularity or increased cellularity is the most difficult criteria to quantify. Thick tissue sections can mimic hypercellular areas and lymphocyte infiltrated areas also appear hypercellular. We used nuclei >53/hpf as the cut off for hypercellularity as proposed by Perry *et al.* (3). Small cell change is sometimes difficult to interpret especially in whorled and hypercelluar areas. Lymphocytic infiltration can cause further confusion. Pseudo brain invasion needs to be distinguished from true brain invasion. Infiltration of tumor cells along with Virchow Robin spaces should not be considered as true brain invasion (3).

In the 2016 WHO classification of CNS tumors, Ki67 labelling index has been introduced as adjuncts in the grading of meningiomas. Review of literature shows many studies using Ki67 percentage on high magnification (X400) in the areas with the greatest degree of immunostaining (9,10,11,12). Ki67LI ranged from 0.73% to 4.07% in grade I and 2.08% to 11.9% in grade II meningiomas (7,10,12-17).

We assessed Ki67 score in four different ways: 1) average Ki67%, 2) highest Ki-67%, 3) Ki67 per hpf average and 4) Ki67 per hpf highest. By all these methods, we found higher Ki67 labelling index in WHO grade II meningiomas as compared to WHO grade I and it was statistically significant. Among the 4 methods, we found counting of Ki67LI by percent in the areas with the highest degree of immunostaining was the most statistically significant (P=0.000). Counting of Ki67LI by per hpf is not reliable because, the number of cells per hpf vary from one field to another. Ki67LI using percentage seems to be more reliable, as the exact numbers of the cells are counted and it is not affected by cellularity in the field.

In our study, we were able to show statistically significant difference in KI67 LI between the grades of meningiomas, but there was overlap with regard to KI67 LI (%) ranges between these groups: grade I (1 - 12), grade II (1 - 30). This overlap in KI67 LI range was seen in other studies also (18,14,19). This may be due to the tumor heterogeneity, the degree of positive immunostaining within the same tumor was extremely variable, with some areas showing a high LI and other areas on the same slide showing very little positive staining. Selection of the block on which to perform immunostaining may have some effect on the KI67 LI and may result in underestimation of the true proliferative potential of the tumor. This overlap between tumor grades may reduce the utility of KI67 LI for meningioma grading in individual cases, particularly if a relatively low KI67 LI is obtained. Thus, correlation with clinical and radiological findings should be done before interpreting KI67 LI.

Tumor recurrence is an inherently described characteristic feature of meningiomas. The varied clinical presentations and diverse histomorphology may be the contributing factors for its perplexing nature. Higher histologic grade, incomplete resection, younger age, specific histologic variants, brain invasion and high proliferation rates are proven risk factors associated with tumor recurrence (3,17,21). Choi Y *et al.,* were of the opinion that grade II meningiomas with Ki67LI of more than 13% should receive post-operative radiotherapy for better local control of tumor (17).

Matsuno *et al.,* (22) found a higher mean Ki67 index in the initial tumor that ultimately recurred (mean Ki67 3.6%) compared to non-recurrent tumors (mean Ki67 1.6%). Abramovich & Prayson (10) also found higher mean Ki67LI in the recurrent group. Matsuno *et al.,* (22) also reported higher mean Ki67LI in recurrent tumors compared to the initial resection specimen. Nakasu *et al.,* reported a cut-off point of 3% for higher recurrence tendency (23). In our study, we could not compare mean KI67 LI between recurrent and non-recurrent groups, because some cases were operated outside for primary (initial tumor) and presented first time in our Institute at the time of recurrence. We found three cases that had primary and recurrent meningioma diagnosed at our Institute. In two of these

cases, we found higher Ki67LI in the recurrent tumor compared to their initial resection specimen.

To summarize, meningothelial (24.6%) followed by transitional meningiomas (24%) were the common histological types observed in this study. The grade II meningiomas accounted for 17.1% of the cases. Fifty percent of atypical meningiomas showed brain invasion and ≥4 mitoses/hpf, while atypical features were seen in 54.1% of cases (exclusively or in association with other features). Atypical features like hypercellularity, sheeting, prominent nucleoli, necrosis, small cell change, papillary change, scattered bizarre nuclei and nuclear pleomorphism were common in grade II in comparison with grade I tumors and was found to be statistically significant. Increased vascularity, lymphocytes and psammoma bodies were commonly observed in grade I meningiomas.

Ki67% (highest) was the most statistically significant LI in differentiating grade I and grade II tumors. Ki67/hpf was less statistically significant compared to Ki67%. The average Ki67/hpf was 5/hpf for grade I and 12/hpf for grade II meningiomas. Ki67/hpf was high in meningothelial, transitional and angiomatous variants bordering on counts found in WHO grade II tumors.

This study had some limitations: 1) Ki67LI could not be performed on all cases in view of limited resources; 2) No case of anaplastic meningioma was encountered during the study period and 3) Dearth of comparison of Ki67LI in recurrent meningiomas (with that of the primary) as some of these cases were initially operated elsewhere.

Conclusion

Meningiomas are a heterogenous group of tumors with morphological overlap between grade I and grade II. Accurate grading of meningiomas is of significance for appropriate management. Ki67LI is a useful adjunct to histomorphology in the diagnosis of meningiomas with values </=4% being associated with indolent behaviour, while Ki67LI >4% pointing towards a higher tumor grade.

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Conflict of Interest

The authors declared that there is no conflict of interest regarding the publication of this article.

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