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Original Research Article

A histomorphological study of meningiomas with relation to Ki-67 proliferative index and review of literature

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ABSTRACT

Objective: The revised 4^{th} edition of the WHO classification of tumours of the central nervous system categorizes meningiomas into three grades based on their histomorphology. However, the biological behaviour and recurrence rates for these tumours cannot be predicted using morphology alone. The aim of the study was to study the demography of Meningiomas and to correlate the grade with the Ki-67 Labelling Index (LI) and compare them to tumour recurrence.

Materials and Methods: The study included 38 cases of Meningioma of various subtypes. Hematoxylin and Eosin slides were reviewed; appropriate blocks were sectioned and stained with Immunohistochemical marker, Ki-67. Slides were studied and Ki-67 labelling index was calculated.

Results: The tumour was more common in the female population and in the 5^{th} and 6^{th} decades of life. The average Ki67 labelling index showed insignificant variation among tumours within the same grade ($p= 0.15$) but demonstrated considerable disparity with increasing grades ($p < 0.01$). There was only one case of recurrence of a previous Papillary Meningioma, with a Ki-67 index of 25.32.

Conclusion: Ki67 labelling index in meningiomas increases in proportion to increasing grade and is a good indicator of tumour recurrence. Some histologically benign tumours have been known to recur after complete excision. Hence, we suggest that immunohistochemistry for Ki-67 LI should be done for all cases of meningioma, irrespective of the type.

1. Introduction

Meningiomas are a group of mostly benign, slow growing neoplasms of the central nervous system that arise from the meningothelial cells of the arachnoid layer of the meninges. They are the commonest non-glial tumour in adults, accounting for about 34% of all intra-cranial tumours.[1] Children are less frequently affected, with meningiomas encompassing only 2.8% of all paediatric primary brain tumours.[2] They commonly occur in the fifth and sixth decades of life with a female predilection of 2:1.[3] Majority of tumours occur within the cranial vault and less commonly in the intraspinal, orbital and epidural areas. Few rare cases of extra-neural occurrence, such as lung, have also been reported.[4]

The revised 4^{th} edition of the WHO classification of tumours of the central nervous system provides guidelines for tumour grading and subtypes. Several variants of meningiomas have been recognised and they are grouped into Grades I, II and III based on their histomorphology. Grade I tumours are those with low proliferative potential and have a possibility of cure after surgical resection alone. They encompass majority of the meningioma subtypes such as meningothelial, fibrous, transtitional, psammomatous, microcystic, angiomatous, secretory and metaplastic. Grade II tumours are infiltrative in nature and may recur, in spite of having a relatively low proliferative activity. They consist of the following histological types, namely, clear cell, chordoid and atypical. Grade III tumours have histological evidence of malignancy, including nuclear atypia and brisk mitotic activity, and such patients would require more aggressive therapy. These include the rhabdoid, papillary

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and anaplastic variants.

Several studies have shown that a grading system based on histomorphological features alone has limitations in predicting the exact biological behaviour of meningiomas.[5,6] This has led to the use of ancillary techniques like proliferation markers to predict tumour progression and recurrence. Ki-67 is one of the most widely used Immunohistochemical proliferative markers that can be used on formalin fixed, paraffin-embedded sections. Reported recurrence rates of histologically benign meningiomas are 7-25% while atypical and anaplastic types have a rate of 29-52% and 50-94%, respectively.[7] Malignant histological features are also associated with a shorter survival period, around 2 to 5 years, depending on the extent of resection.[8,9] However, studies have suggested that, irrespective of the histological grade, meningiomas having an index of $>$ 4% have an increased risk of recurrence similar to that of atypical meningioma, while those tumours with an index of $>$ 20% are associated with death rates comparable to that of anaplastic meningioma.[5]

The aim of our study was to investigate all cases of meningiomas received in our department in order to record the demographic details, frequency and location of the various subtypes of meningioma and grade them based on the recent WHO classification (2016). We also attempted to correlate the grade with the Ki-67 Labelling Index (LI) and compare them to tumour recurrence.

2. Materials and Methods

The study was conducted in Saveetha Medical College, a tertiary care institute in Chennai, India after obtaining necessary approval from the Institutional Research Board. It was a retrospective study and complete enumeration sampling technique was used. All cases of meningioma received and reported in the Department of Pathology during a period of five years from 2013 to 2018 were collected. Case details, such as age, gender and location of the tumour, were noted from the case records of the patient maintained in the medical records section, after prior permission. The appropriate H&E stained slides were retrieved from the Histopathology division. The H&E slides were reviewed and the histological features were noted. The tumours were diagnosed and graded accordingly, based on the 2016 WHO classification of tumours of the central nervous system. Appropriate blocks were selected for Immunohistochemical staining with Ki- 67 proliferative marker. Blocks found unsuitable for sectioning due to physical disintegration were excluded. 4μm thick tissue sections were taken on to slides coated with Poly L Lysine. The Primary antibody used was Ki-67 (MIB-1) monoclonal antibody, 1:50, DAKO, USA and the secondary antibody kit was Novolink polymer (Leica Biosystems). Positive and negative controls were used during the staining procedure.

Scoring was done by evaluating the percentage of tumour cell nuclei that were stained. For each immunostained slide, digital images of 10 or more fields located within the tumour was captured using a Magcam DC5 camera attached to an Olympus CX 21i microscope with 400X objective. The cells were then counted using Adobe Photoshop application. A minimum of 1000 tumour cells were counted for each slide.

3. Results

There were a total of 39 cases of meningiomas of different histologic types and grades. All the cases were stained with Ki-67 immunohistochemistry. Only 38 cases were included in the study, the excluded case showed post-radiotherapy changes and could not be categorized into any variant based on the histopathology.

In our study, we noted a slight female preponderance in all grades. The tumour was more common in the 5^{th} and 6^{th} decades of life. We had only one case of paediatric meningioma, which was diagnosed as a grade I tumour. Convexity of the cerebrum was the commonest site in all grades of tumour and Grade I tumours were commonest in all sites.(Table 1)

Meningothelial meningioma was the most common variant overall, followed by transitional and fibrous types. We did not diagnose any case of secretory, metaplastic, clear cell or rhabdoid meningiomas. Among Grade I meningiomas, both the lowest and the highest Ki67 values were seen in m eningothelial meningioma. The lowest and highest values in grade II tumours were noted in chordoid and atypical meningioma respectively. The lowest value of Ki67 LI in Grade III tumours was seen in anaplastic and highest value in papillary type.(Table 2) The overall lowest and highest values was seen in meningothelial meningioma (0.45) and papillary Meningioma (25.32) respectively (Figure 2) Average Ki67 LI was calculated for each variant and plotted. The graph showed insignificant variation of Ki67 LI among tumours within the same grade but significant variation across grades. (Figure 1) Average Ki67 LI for Grade I tumours was less than 7% with the exception of one case, which showed 12.83% (Figure 3). The average Ki 67 LI for grades II and III were 13.88 and 2 2.84% respectively. The 'P' value for the Ki67 LI among different grades was calculated using ANOVA, which was a significant value of $<$0.01.(Table 3) There is a nearly linear correlation of Ki67 LI to the grade of meningioma.

4. Discussion

In this present study, there were a total of 38 cases of meningioma. There are inconsistent reports regarding the influence of age and gender on the grade of meningioma. Ilidian *et al*, reported that both variables have no influence on proliferative activity.[10] However, Kasuya *et al*, reported that male gender was an independent risk factor for high

Table 1: Comparison of Age, Genderand Location in different tumour grades

Gender	**Grade I**	**Grade II**	**Grade III**	**Total (%)**
Male	12	1	3	16(42.1%)
Female	18	2	2	22 (57.9%)
Age	**Grade I**	**Grade II**	**Grade II**	**Total**
≤18 years	1	0	0	1 (2.63%)
19-40 years	6	0	2	8 (21.05%)
41-60 years	21	3	2	26 (68.42%)
≥61 years	2	0	1	3 (7.90%)
Location	**Grade I**	**Grade II**	**Grade III**	**Total**
Convex/cerebral	15	1	2	18
Sphenoid	1	-	1	2
Spinal	3	1	-	4
Tentorial	-	-	1	1
Falx	2	1	1	4
Parasaggital	3	-	-	3
Basal	4	-	-	4
Suprasellar	2	-	-	2
Total (%)	30 (78.9%)	3 (7.9%%)	5 (13.2%)	38 (100%)

Table 2: Ki67 values in varioustumour subtypes

Sub Type	**No. of cases**	**%**	**Minimum Ki67 LI**	**Maximum Ki67 LI**	**Average Ki67 LI**
Meningothelial	11	28.9%	0.45	12.83	5.27
Fibrous	7	18.4%	3.54	6.47	4.81
Transitional	7	18.4%	3.29	8.09	5.41
Psammomatous	2	5.3%	3.53	5.04	4.28
Microcystic	2	5.3%	4.85	6.03	5.44
Angiomatous	1	2.6%	4.73	4.73	4.73
Chordoid	2	5.3%	8.97	13.72	11.35
Atypical	1	2.6%	16.41	16.41	16.41
Papillary	2	5.3%	23.66	25.32	24.49
Anaplastic	3	7.9%	18.72	24.38	21.47
Total	38	100%	0.45	25.32	24.49

Ki67 LI : Ki67Labelling index, % - percentage of cases

Table 3: Correlation of Ki67 LI withthe grades of Meningioma (WHO 2016)

Grade	**Minimum Ki67 LI**	**Maximum Ki67 LI**	**Average Ki67 LI**	**value (ANOVA)**
I	0.45	12.83	4.99	
II	8.97	16.41	13.88	<0.01 (Significant)
III	18.72	25.32	22.84	

Ki67 LI : Ki67 Labelling Index

proliferative potential.[11] We reported no relevant findings in our study regarding the role of age and gender in the grade of the tumour.

The biological nature of meningiomas is a complexentity. They can be completely benign, can show atypical features with increased risk of progression or can be frankly malignant tumours with high rates of recurrence, metastasis and mortality.

Grading has been implicated as an important tool to decide for patient management. Grade I tumours are considered to be benign and are treated with surgery alone whereas Grade II and III are treated with surgery, radiotherapy and chemotherapy based on the extent and atypia.[12,13] It also helps to assess the possibility of recurrence and can be correlated with the prognosis.[14,15] However, it is not necessary that all variants under the same grade should exhibit the same behaviour.[16] Moreover,

Table 4: Comparison of average Ki67in each subtype with another study

Variant	Present Study (Average Ki67 LI ± 2SD)	Babu S et al (2011) (Average Ki67 LI ± 2SD)
Meningothelial	5.27 ± 3.45	4.63 ± 3.44
Fibrous	4.91 ± 0.98	2.46 ± 2.73
Transtitional	5.41 ± 1.71	4.35 ± 3.87
Psammomatous	4.28 ± 0.75	3.75 ± 4.12
Microcystic	5.44 ± 0.82	2.16 ± 1.37
Angiomatous	4.73 ± 0.0	7.66 ± 6.59
Chordoid	11.33 ± 2.36	8.92 ± 7.57
Atypical	16.41 ± 0.0	11.28 ± 7.08
Papillary	24.49 ± 0.83	18. 33 ± 10.4
Anaplastic	21.47 ± 2.31	19.81 ± 7.08

Ki67 LI: Ki67Labelling Index, SD: Standard deviation

Table 5: Comparison of average Ki67in each grade with other studies

Grade	I	II	III
Present Study	4.99	13.88	22.98
Ramesh Babu et al (2016)	3.1	7	14.2
N. Shayanfer et al (2010)	2.98	9.30	34
Roser F et al (2004)	3.88	9.95	12.18

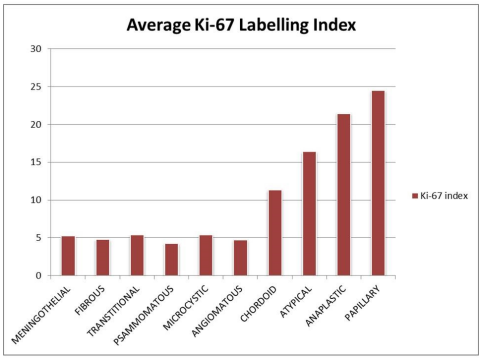

Fig. 1: Average ki-67 labelling index among different subtypes (WHO 2016)

important factors such as invasion and recurrence cannot be predicted based on clinical and histomorphological features alone. Grading of meningiomas was updated in the recent 2016 WHO classification of CNS tumours and we have used the recent grading system to classify the tumours. Roser et al., published a retrospective study of 600 resected meningiomas in which histological grading revealed 91% of the cases to be WHO grade I meningioma, 7% as grade II meningioma and 2% as grade III meningioma.[17] These values were similar to various other studies.[18–20] Our series showed an almost analogous result, with grade I being the most common (79.2%). However, frequency of grade III tumors (13.2%) was slightly higher than grade II tumors (7.9%). This can be possibly attributed to our application of the recent WHO grading system (2016) while the other studies were published much before it.

Ki67 LI is a marker used to assess the proliferative potential of a tumour and it correlates with histological grade and recurrence. Generally, cellular proliferation increases in proportion to the grade and Ki-67 proliferation index correlates approximately with the volume growth rate. Several studies have shown that increased Ki-67 index was associated with an increased risk of recurrence.[21] In a study conducted by Kolles et al., it was established that Ki-67 LI is the most important criterion for differentiating anaplastic meningiomas (mean Ki-67 LI: 11%) from WHO grade I tumours (mean Ki-67 LI: 0.7%)[22] There was no significant difference in the Ki67 LI between the histological subtypes within each grade in our study and that is in agreement with the observations made by Babu et al.[16] (Table 4) The average Ki67 LI in our series showed a statistically significant and linear increase with the grades I, II and III. This finding is similar to other reports.[14–17,23](Table 5)

Recurrence after seemingly total resection is one of the most prevalent problems in the management of Meningiomas.[24] In our series, out of 38 cases of meningioma, one case was found to be recurrent. It was initially diagnosed as papillary meningioma. Following complete resection of the mass, the patient underwent radiotherapy based on the tumour grade. Retrospective analysis of the initial tumour showed a high Ki-67 LI of 25.32%. The tumour recurred within 2 years and presented as an unclassifiable meningioma with post-radiotherapy changes. IHC staining with Ki-67 was done and an

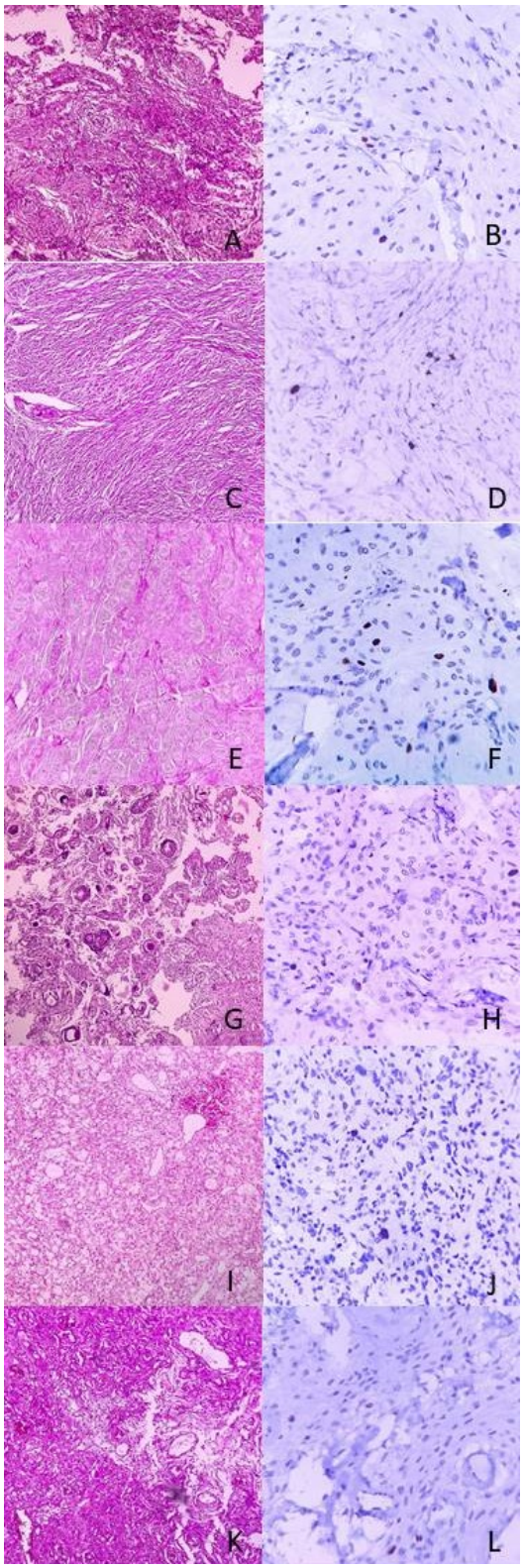

Fig. 2: Grade I tumours with corresponding average Ki67 labelling index.; **A):** Meningothelial (H&E, 100X); **B):** Ki67 (IHC, 400X); **C):**) Fibrous (H&E,100X); **D):** Ki67 (IHC, 400X); **E):** Transitional(H&E, 100X); **F):** Ki67 (IHC, 400X); **G):** Psammomatous(H&E, 100X); **H):** Ki67(IHC, 400X); **I):** Microcystic(H&E, 100X); **J):**Ki67 (IHC, 400X); **K):** Angiomatous I) Ki67 (IHC, 400X)

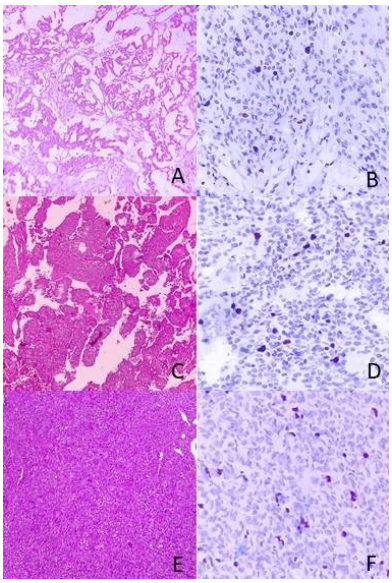

Fig. 3: Grade II and III tumors with corresponding average Ki67 labelling index; **A):** Chordoid (H&E, 100X); **B):** Ki67(IHC, 400X); **C):** Papillary (H&E, 100X); **D):** Ki67 (IHC, 400X)E) Anaplastic (H&E,100X) F) Ki67 (IHC, 400X)

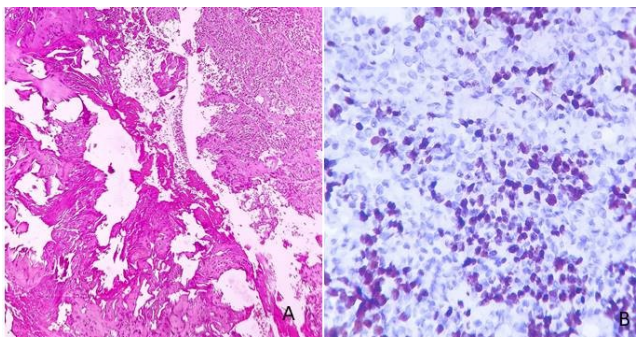

Fig. 4: A): Meningioma with postradiotherapy changes (H&E, 100X); **B):** Ki67 (IHC, 400X)

abnormally high value (>70%) was noted (Figure 4). The slide was not included in the study due to difficulty in describing the recurrent variant. It can be interpreted from this particular case that an increased Ki67 LI is a predictor of recurrence. There are contradicting views on this statement in literature. Perry *et al* suggested that Ki67 LI in excess of 4.2% was an accurate predictor of high tumour proliferation activity and recurrence.[9] Ho *et al*, suggested a cut-off value of 10 for Ki67 LI as the most precise indicator of recurrence.[2,25] In a study by Maes *et al*, it was suggested

that Ki67 was a good marker of proliferation potential but not a good predictor of recurrence due to lack of statistically significant differences between recurrent and non-recurrent tumours. The number of recurrent cases in our study was very small and not adequate to arrive at a note-worthy conclusion.

5. Conclusion

In conclusion, the Ki67 labelling index in meningiomas increases in proportionate with increasing grade and is a good indicator of tumour recurrence. Some histologically benign tumours have been known to recur after complete excision. Hence, we suggest that immunohistochemistry for Ki-67 LI should be done for all cases of meningioma, irrespective of the type.

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None.

8. Conflict of interest

The authors declare no conflict of interest.

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