

Association of meningioma grade with Ki-67 proliferative index – an institutional study

Sara Babar, Yousra Zahid, Humaira Erum, Atif Ali Hashmi, Naveen Mubarak Faridi, Muhammad Irfan

Liaquat National Hospital, Karachi Pakistan

ABSTRACT

Objective: To evaluate the frequency and association of Ki-67 labelling index with tumor grade in Meningioma.

Material and Methods: This cross sectional study was conducted at the Department of Histopathology, Liaquat National Hospital Karachi from 1st July 2024 to 31st December 2024. A total of 107 Meningiomas that underwent resection were included in this study. After determining tumor type histologically, immuno-staining for Ki-67 markers was performed. The association between the Ki-67 index and WHO grade of Meningioma was assessed. All data was systematically recorded in a pre-structured proforma.

Result: The average age at diagnosis was 48.99(14.44) years, with female predominance (60.7%). At the time of diagnosis, most tumors were grade 1 (59.8%), and meningothelial Meningioma (55.1%) was the most-common tumor type. A significant association of WHO grade was noted with Ki-67 index. The mean Ki-67 index for WHO grade 3 is significantly (20%) higher than that of grade 1 (3.86%) and grade 2 (7.34%).

Conclusion: Ki-67 was significantly associated with WHO grade ($p = <0.001$). It is also associated with tumor type, number of mitosis and pattern less or sheet like growth ($p = <0.001$) helps in understanding tumor behavior and its potential prognosis. We observed that Meningiomas were more prevalent among the female population, and grade 3 Meningiomas showed an increased expression of Ki-67 index. Therefore, Ki-67 index can be used for prognostic stratification of Meningioma.

Keywords: Ki-67 Index, Meningioma, Brain tumor

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INTRODUCTION

Overall, brain tumors are rare compared with other types of cancer. Brain tumors are the 19th most common cancer occurring worldwide and is characterized by high mortality, mostly in developing countries. The GLOBOCAN project estimated approximately 321,731 new cases in 2022, with 248,500 deaths reported globally [1].

Among all the tumors in the central nervous system, Meningiomas are the most common primary central nervous tumor, accounting for approximately 37.6% and

approximately 50% of all benign brain tumors [2]. Most Meningiomas are benign and originate from the meningeal layers of either the brain or spinal cord [3]. The exact cause of Meningiomas is not fully understood; however, the risk of Meningioma dramatically increases with increasing age, female sex, African American ethnicity, genetics, and increased body mass index. Currently, Meningioma is most commonly due to radiation exposure to the head region [4].

Meningiomas are usually slow-growing tumors that can transform into malignant tumors. According to the WHO classification system, Meningiomas are classified into 1 of 3 grades based on their histological characteristics such as mitotic activity, necrosis and architectural patterns. Grade 1 Meningiomas are benign and least aggressive, with slow growth and low recurrence rate. They are mostly asymptomatic and require close monitoring. If symptoms are

Correspondence: Dr. Yousra Zahid, Senior Registrar, Department of Histopathology, Liaquat National Hospital, Karachi Pakistan

Email: yzahid07@yahoo.com

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present, the mainstay of treatment is surgical removal of entire tumor. Grade 2 includes Meningiomas that have atypical features, and due to their high rate of recurrence adjuvant radiation therapy is recommended after surgery. Grade 3 are high-grade Meningiomas with anaplastic features and are considerably more aggressive and have metastatic potential [5]. Grade-3 requires both combination of surgery and radiation therapy and other therapies like chemotherapy [6, 7]. Apart from its histological features, there is no establish biomarkers to predict tumor grade in Meningioma. Ki-67 is the most widely used immunohistochemistry marker to determine predictive index of tumors. It is a non-histone protein that is expressed in the proliferative phase of the cell cycle [8].

Data regarding the correlation of grade with Ki-67 in Meningioma is scarcely available worldwide and data from Pakistan is lacking. We evaluated the frequency and association of Ki-67 labeling index with tumor grade in Meningioma. As a rare form of neoplasm, limited studies have been conducted to determine the association of Meningiomas grade in relation to Ki-67. As tumor characteristics differ in different populations based on genetic profile and risk factors, it is of cardinal importance to evaluate such an association in our population. This study is of immense importance for surgeons and oncologists.

MATERIAL AND METHODS

This cross-sectional study was conducted at the Department of Histopathology Liaquat National Hospital – Karachi from 1st July 2024 – 31st December 2024 after taking the approval from institutional review board vide reference number App# 1042-2024-LNH-ERC dated 11 June 2024. Sample size was calculated by WHO sample size calculator by taking prevalence of Ki-67 < 5% = 51% [9], Margin of error = 10% thus calculating sample size was 96 at 95% confidence interval. We take sample size of 101 patients. Non-probability consecutive sampling technique was used to collect the data

Biopsy proven cases of Meningioma (all variants) of both genders, irrespective of age.

Patient with inadequate clinical details, autolyzed sample and brain tumors other than meningioma were excluded from study

The study was undertaken after receiving an endorsement from the institutional research and ethics committee. Patients who met the inclusion criteria were selected for the study. Informed consent was taken for patients' participation and the use of their data in research. A concise medical history of the disease was collected. The principal investigator took clinical histories from all the patients. Specimen coded as meningioma was received, and after labeling and data entry, a gross examination of the tissue was done. Entire tissue samples were submitted and processed as paraffin-embedded blocks. Hematoxylin and Eosin-stained examination glass slides were prepared and screened microscopically to assess tumor type, tumor grade, and tumor variant. While confirming the diagnosis of Meningioma, special and immunohistochemical stains (Ki67) were performed.

Number of positively stained (nuclear staining) tumor cells were measured in 10 HPFs in 10 different areas of tumor and an average labelling index was calculated.

Data about age, gender, specimen size, and tumor grade and paraffin section diagnosis were recorded in a pre-designed Performa by the Principle Investigator. Confounding variables as well as biases were controlled by strictly following the inclusion and exclusion criteria. Patient confidentiality will be maintained by removing all patient identifying information from the Performa's and data sheets.

Patient data will be compiled and analyzed using the statistical package for Social Sciences (SPSS) Version 25. Frequency and percentage were computed for qualitative variables like gender, histological type, histological variant, histological grade, and brain invasion. Normality Of the data was checked by the Shapiro–Wilk test. Mean±SD will be calculated for quantitative variables, i.e., age, number of mitosis, and Ki67. Median (IQR) values were calculated if the data were not normal. Student's t-test or ANOVA was used to determine the mean difference of age, number

of mitosis, and Ki-67 among categorical variables (as appropriate). Chi-square or Fisher's exact test (if freq < 5) was applied to find associations between categorical variables such as Histological grade and ki-67 categories. A P-value ≤ 0.05 was considered significant.

RESULTS

The descriptive data of all 107 patients included in this study are described in Table-I. It was noted that approximately 65 (60.7%) patients were female. The mean age was found to be 48.99 (14.44) years. We found that Meningioma was more prevalent (60.7%) in adults aged >45 years. There were 64(59.8%) grade 1, 41(38.3%) grade 2, and 2(1.9%) grade 3 Meningiomas. The most common subtype of Meningioma was meningothelial Meningioma, and approximately 59(55.1%) of cases were observed. Similarly, hyper cellularity, pattern less growth, necrosis, macro nucleoli, small cell components, and brain invasion were present in 13.1%, 7.5%, 14%, 4.7%, 3.7%, and 13.1% of patients, respectively. There were 58(54.2%) patients with ki-67 index <5%, 33(30.8%) with ki-67 index 5-9% and 16(15%) with ki-67 $\geq 10\%$.

Determining mean difference of Ki67 index with tumor type of Meningioma. Anaplastic Meningioma ($20.00 \pm 0.00\%$) and atypical Meningioma ($7.61 \pm 3.16\%$) showed a significantly higher Ki-67 index compared to other Meningioma variants Association of Ki-67 index with tumor grade, shows the mean difference of Ki-67 indexes with tumor grade. The Mean Ki-67 of grade 3 is significantly ($20 \pm 0.000\%$) higher than that of grade 1 ($3.86 \pm 2.15\%$) and grade 2 ($7.34 \pm 3.27\%$) as presented in Table-II.

Table-III determining significant association of Ki-67 index with tumor type, number of mitosis, pattern less growth and WHO grade. No significant alliance of Ki-67 was recorded with age, gender, brain invasion, hyper cellularity, necrosis, macro nucleoli and small cell component. Atypical and anaplastic Meningioma showed a significantly higher Ki-67 index than that of other variants of Meningioma. Only 4 cases of pattern less growth was seen with Ki-67 index >10%. All grade 3 Meningiomas had a Ki-67 index >10%". Similarly, 75% of grade 2 Meningioma showed a Ki-67 higher than 10%.

Table-I- Descriptive statistics of study population (n=107).

Variables	Values
Gender	
Male, n (%)	42 (39.3)
Female, n (%)	65 (60.7)
Age (years)	
Mean (SD)	48.99(14.44)
Groups	
≤ 45 years, n (%)	42 (39.3)
> 45 years, n (%)	65 (60.7)
Number of mitosis	
Mean (SD)	2.76(3.21)
Groups	
< 4	82 (76.6)
4-19	23 (21.5)
≥ 20	2 (1.9)
Tumor Type	
Meningothelial Meningioma, n (%)	59 (55.1)
Atypical Meningioma, n (%)	36 (33.6)
Anaplastic Meningioma, n (%)	2 (1.9)
Angiomatous Meningioma, n (%)	2 (1.9)
Psammomatous Meningioma, n (%)	6 (5.6)
Clear cell Meningioma, n (%)	2 (1.9)
Brain Invasion	
Present, n (%)	14 (13.1)
Absent, n (%)	93 (86.9)
Hypercellularity	
Present, n (%)	14 (13.1)

Absent, n (%)	93 (86.9)
Pattern less growth	
Present, n (%)	8 (7.5)
Absent, n (%)	99 (92.5)
Necrosis	
Present, n (%)	15 (14)
Absent, n (%)	92 (86)
Macro nucleoli	
Present, n (%)	5 (4.7)
Absent, n (%)	102 (95.3)
Small Cell Component	
Present, n (%)	4 (3.7)
Absent, n (%)	103 (96.3)
WHO Grade	
Grade 1, n (%)	64 (59.8)
Grade 2, n (%)	41 (38.3)
Grade 3, n (%)	2 (1.9)
Ki67 (%)	
Mean± SD	5.50±3.70
Groups	
<5%, n (%)	58 (54.2)
5-9%, n (%)	33 (30.8)
≥10%, n (%)	16 (15)

Table-II: Mean Ki67 according to grade and type.

Variables	Mean (SD)	p-value
WHO Grade		
Grade 1	3.86(2.15)	<0.001*
Grade 2	7.34(3.27)	
Grade 3	20.00(0.00)	
Tumor Type		
Meningothelial Meningioma	3.93(2.33)	<0.001*
Atypical Meningioma	7.61(3.16)	
Anaplastic Meningioma	20.00(0.00)	
Angiomatous Meningioma	2.50(0.70)	
Psammomatous Meningioma	4.83(2.56)	
Clear cell Meningioma	4.00(1.41)	

SD; Standard deviation, One way ANOVA was applied , P-value≤0.05 considered as significant, *Significant at 0.05 levels

Table-III: Association of Ki-67 with Clinic pathological parameter.

Variables	Values			P-value
	KI67			
	<5%	5-9%	>=10%	
Gender				
Male, n (%)	17 (29.3)	16 (48.5)	9 (56.3)	0.063
Female, n (%)	41 (70.7)	17 (51.5)	7 (43.8)	
Age Groups				
≤45 years, n (%)	21 (36.2)	14 (42.4)	7 (43.8)	0.779
>45 years n (%)	37 (63.8)	19 (57.6)	9 (56.3)	
Number of mitosis				
<4	55 (94.8)	24 (72.7)	3 (18.8)	<0.001*
4-19	3 (5.2)	9 (27.3)	11 (68.8)	
≥20	0 (0)	0 (0)	2 (12.5)	
Tumor Type				
Meningioma meningothelial, n (%)	45 (77.6)	11 (33.3)	3 (18.8)	<0.001*
Atypical Meningioma, n (%)	7 (12.1)	18 (54.5)	11 (68.8)	
Anaplastic Meningioma, n (%)	0 (0)	0 (0)	2 (12.5)	
Angiomatous Meningioma, n (%)	2 (3.4)	0 (0)	0 (0)	
Psammomatous Meningioma, n (%)	3 (5.2)	3 (9.1)	0 (0)	
Clear cell Meningioma, n (%)	1 (1.7)	1 (3)	0 (0)	
Brain Invasion				

Present, n (%)	5 (8.6)	6 (18.2)	3 (18.8)	0.301
Absent, n (%)	53 (91.4)	27 (81.8)	13 (81.3)	
Hypercellularity				
Present, n (%)	4 (6.9)	7 (21.1)	3 (18.8)	0.103
Absent, n (%)	54 (93.1)	26 (78.8)	13 (81.3)	
Pattern less growth				
Present, n (%)	0 (0)	4 (12.1)	4 (25)	<0.001*
Absent, n (%)	58 (100)	29 (87.9)	12 (75)	
Necrosis				
Present, n (%)	5 (8.6)	7 (21.2)	3 (18.8)	0.197
Absent, n (%)	53 (91.4)	26 (78.8)	13 (81.3)	
Macro nucleoli				
Present, n (%)	1 (1.7)	2 (6.1)	2 (12.5)	0.095
Absent, n (%)	57 (98.3)	31 (93.9)	14 (87.5)	
Small Cell Component				
Present, n (%)	2 (3.4)	2 (6.1)	0 (0)	0.803
Absent, n (%)	56 (96.6)	31 (93.9)	16 (100)	
WHO Grade				
Grade 1, n (%)	48 (82.8)	14 (42.4)	2 (12.5)	<0.001*
Grade 2, n (%)	10 (17.2)	19 (57.6)	12 (75)	
Grade 3, n (%)	0 (0)	0 (0)	2 (12.5)	

Chi-square/ fisher exact test was applied, P-values≤0.05 considered as significant, *Significant at 0.05 levels

DISCUSSION

There has been ongoing debate about Ki-67 index in predicting the prognosis of Meningiomas. While histologic grading is widely recognized as a crucial prognostic factor, the exact significance of Ki-67 in this context remains unclear. The study aims to explore the alliance between the WHO grade and the Ki-67 index in Meningiomas. Significant association between Ki-67 and WHO grade was determined. The average Ki-67 of grade 3 is significantly (20%) higher than that of grade 1 (3.86%) and grade 2 (7.34%).

Bhagyalakshmi *et al.*, [10] conducted a study in an Andhra Pradesh medical college on 50 patients between October 2017 and September 2019 showed that the average Ki-67 index of Grade I Meningiomas was 2.3%, Grade II Meningiomas was 7.3%, and Grade III Meningiomas showed a Ki-67 index of 21% and almost similar findings were seen in our study. Liu N *et al.*, [11] conducted a study on histopathological spectrum of Meningioma with ki-67 showed higher Ki-67 index associated with higher grade of Meningioma. Sashidhar *et al.*, [12] correlated Ki-67 with histological grade suggested that higher Ki-67 index indicates higher grade of Meningioma. Another study conducted by Pugonja *et al.*, [13] in Zenica from 2010 to 2020 suggesting that higher tumor grade was associated with increase expression

of Ki-67. Yeldir *et al.*, [14] conducted a study that has similar findings to our study, shows an increased expression of Ki-67 is associated with a higher grade of Meningioma.

Telugu *et al.*, [9] studied 224 consecutive patients with Meningioma to predict the association of Ki-67 index with tumor grade. He found that Ki-67 index was mostly increased in grade 3 followed by grade 2 Meningiomas. As in our study we had only 2 cases of grade 3 Meningioma and both having Ki-67 index of ≥10%

The study states association of Ki-67 index with tumor type. Mostly the Meningiomas are benign, histologically different subtypes are associated with aggressiveness. We found high Ki-67 index in atypical Meningioma (68.8%). These results are also supported by various studies. One study which was conducted in Turkey by Küçükosmanoğlu *et al.*, [15] shows 8 cases of atypical Meningioma showed an increased Ki-67 index of 12.75%.

Behling *et al.*, [16] retrospective study on 1718 Meningioma cases, and 6.7% showed brain invasion and correlation between invasion and a higher Ki-67 index. Although we failed to find an association between brain invasion and the Ki-67 index. Three cases of brain invasion with increased Ki-67 were eventually found in the study.

LIMITATIONS

Major limitation of the study includes: Limited sample size. The long-term clinical outcome of the patients was not recorded and lack of interobserver validation for Ki-67 scoring. Moreover, we did not evaluate the association of various biomarkers with Meningiomas and lack of molecular characterization (e.g., NF2 status).

CONCLUSION

Association of Ki-67 index was found with tumor grade. It is also associated with specific tumor characteristics such as tumor type, number of mitosis and pattern less growth. We observed that Meningiomas were more prevalent in patients aged >45 years in our region, with female predominance irrespective of the grade. Anaplastic and atypical Meningiomas show increased expression of the Ki-67 index.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Sara Babar: Substantial contributions to study design, acquisition of data, questionnaire design manuscript drafting, final approval of the draft version, agree to be accountable for all aspects of the work

Yousra Zahid: Substantial contributions to analysis and interpretation of data, final approval of the draft version, agree to be accountable for all aspects of the work

Humaira Erum: Substantial contributions to acquisition of data, data collection, revisions, final approval of the draft version, agree to be accountable for all aspects of the work

Atif Ali Hashmi: Manuscript writing, reviewing it critical for important intellectual Content, final approval of the draft version, agree to be accountable for all aspects of the work

Naveen Mubarak Faridi: Analysis and interpretation of data, Critical review, final approval of the draft version, agree to be accountable for all aspects of the work

Muhammad Irfan: Critical review, final approval of the draft version, agree to be accountable for all aspects of the work

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