DOI: 10.7860/JCDR/2025/76074.20929

Original Article

Pathology Section

Immunohistochemical Analysis of Progesterone Receptor and Ki-67 in Meningioma: A Cross-sectional Study

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ABSTRACT

Introduction: The most common primary intracranial tumour is meningioma. It occurs mostly in middle-aged to elderly individuals. Differentiating meningiomas from other intracranial lesions and properly grading them is often a challenging task for pathologists. Meningiomas can cause significant morbidity, mortality, and recurrence, even after complete excision, which may lead to repeat operations and ultimately reduced survival rates. Meningiomas are categorised by the World Health Organisation (WHO) into three grades, primarily based on subjective methods that consider morphology, mitotic figures, and necrosis. Proliferative activity can also be assessed to some extent using these parameters. To minimise subjective biases, it is advisable to use Progesterone Receptor (PR) expression and Ki-67 Labelling Index (LI)-when feasible-as predictive markers for understanding tumour behaviour, which can also be useful for individualised management.

Aim: To investigate the status of PR expression and the Ki-67 index in meningioma, along with their associations with age, gender, risk factors, histological types, and grading of meningiomas.

Materials and Methods: The present study was a Institution-based retrospective cross-sectional analysis conducted in the Department of Pathology in collaboration with the Department of Neurosurgery at Nil Ratan Sircar Medical College and Hospital (NRSMCH), Kolkata, West Bengal, India. The study examined the correlation of PR expression with Ki-67 LI in 50 diagnosed cases of meningiomas following a retrospective review of all cases from March 2022 to February 2023. Primary ready-to-use antibodies were employed immunohistochemically to assess the immunostatus of these markers for prognostication of meningiomas. For statistical analysis, Statistical Package for Social Sciences (SPSS) version 27.0 was utilised, applying mean, Standard Deviation (SD), Analysis of Variance (ANOVA), and Chi-square testing. A p-value of less than 0.05 was considered statistically significant.

Results: Among the 50 cases, there were 30 Females (F) and 20 Males (M), resulting in a ratio of M:F=1:1.5. The percentage distribution of grade I, grade II, and grade III cases was 37 (74%), 10 (20%), and 3 (6%), respectively. Meningothelial tumours were the predominant histomorphological subtype, accounting for 14 cases (37.83%). PR positivity was observed in 35 cases (70%). Most of the grade I cases demonstrated PR positivity (26 out of 37 cases, or 70.27%) and a low mean Ki-67 value of 4.16%. In contrast, the grade III cases primarily exhibited absent to weakly positive PR status (3 out of 3, or 100%) with a high Ki-67 value of 11%. The mean Ki-67 value was higher in PR-negative cases (n=15), at 7.18% with an SD of 4.26, while it was lower in PR-positive cases (n=35), with a mean of 3.64% and an SD of 4.17. Both PR expression and Ki-67 index showed a significant reduction and increase, respectively, with increasing WHO grades. The association of grade with PR and Ki-67 was significant (p-value=0.003 and p-value=0.004, respectively). An inverse correlation was observed between the Ki-67 index and PR score (R=-0.7561). The combined PR status and Ki-67 expression had a sensitivity of 96.67%, specificity of 100%, and an overall accuracy of 97.78%.

Conclusion: The results indicate that middle-aged females are more likely to develop meningiomas, with the most common site being intracranial. Grade I tumours were the most prevalent, particularly the meningothelial subtype. PR expression decreased, and Ki-67 index increased with higher grades. The mean Ki-67 value was greater in grade III meningiomas and PR-negative cases. The association between tumour grade and PR and Ki-67 was significant. The study of PR and Ki-67 immunohistochemical staining proved to be valuable supplements to routine histopathological assessments; thus, management strategies should be individualised.

Keywords: Immunostains, Intracranial, Grade, Tumours

INTRODUCTION

Meningiomas are benign tumours attached to the dura mater, and most cases are slow-growing in nature. They arise from arachnoid cells. Meningiomas account for 18% of all primary intracranial tumours and 25% of all intraspinal tumours [1,2]. These tumours occur most frequently in middle-aged to elderly women [2]. Females are affected more than males, and the growth rate is higher in females, possibly due to relative hormonal excess during pregnancy or the luteal phase of the menstrual cycle [2]. Radiation exposure, trauma, and genetic factors are also responsible for the development of meningiomas [1]. The clinical presentation depends on the location of the tumour [2].

Although most cases are benign, some histological types can be lethal, making it a challenging task for pathologists to determine which variant will recur. In this context, the question of prognosis arises. Important factors include tumour grade and various immunological parameters, such as Oestrogen Receptor (ER), PR, and Ki-67 LI. The WHO classifies meningiomas into three categories: typical, atypical, and anaplastic (grades I, II, and III, respectively) [2].

Some types of meningiomas have a low risk of recurrence and aggressiveness, such as meningothelial, transitional, psammomatous, angiomatous, microcystic, fibroblastic, secretory, lymphoplasmacyte-rich, and metaplastic meningiomas [2]. Conversely, types such as clear cell, papillary, rhabdoid, and chordoid varieties show a greater likelihood of recurrence [2]. The new WHO 2021 classification for grading meningiomas has introduced criteria regarding brain invasion and various molecular markers as new diagnostic criteria for Grade II or atypical meningiomas [2].

It is now emphasised that the criteria defining atypical or anaplastic (i.e., Grades II and III) meningiomas should be applied regardless of the underlying subtype. As noted in prior classifications, chordoid and clear cell meningiomas are associated with a higher likelihood of recurrence than the average CNS WHO Grade I meningiomas and have been assigned to CNS WHO Grade II; however, larger and prospective studies would be beneficial to validate these CNS WHO Grade II assignments and to identify additional prognostic biomarkers.

Historically, rhabdoid and papillary morphologies qualified for CNS WHO Grade III, regardless of other indications of malignancy. While papillary and rhabdoid features are often seen in conjunction with other aggressive characteristics, more recent studies suggest that the grading of these tumours should not be based solely on rhabdoid cytology or papillary architecture. Several molecular biomarkers are also associated with the classification and grading of meningiomas, including SMARCE1 (clear cell subtype), BAP1 (rhabdoid and papillary subtypes), and KLF4/TRAF7 (secretory subtype) mutations, TERT promoter mutations and/or homozygous deletions of CDKN2A/B (CNS WHO Grade III), loss of nuclear expression of H3K27me3 (potentially indicating worse prognosis), and methylome profiling (prognostic subtyping) [2].

Progesterone is encoded by a single PGR gene on chromosome 11q22. It has two isoforms, PR-A and PR-B. PR-B is the positive regulator of the effect of progesterone, while PR-A is the negative regulator of the same [2]. The expression of PR is inversely related to the progression of meningioma. Ki-67 is strongly associated with tumour cell proliferation and growth [2]. Its expression increases in most malignant cases. It is also used to grade meningiomas and to predict prognosis as well as aggressiveness [2].

The present study was aimed to investigate the association of age, sex, risk factors, histological types, and grading of meningioma with PR immunostaining and Ki-67 immunostaining and to determine the correlation of PR with Ki-67 in meningioma.

MATERIALS AND METHODS

The present study was an Institution-based retrospective cross-sectional study, conducted in the Department of Pathology in collaboration with the Department of Neurosurgery of Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India. It included 50 meningiomas with relevant clinical data from March 2022 to February 2023, after obtaining the necessary ethical committee permission from the institution (Memo number: NO/NMC/693, dated 10.02.2024). The following necessary materials were retrieved from the histopathology record to precede the study: patients' case notes, histology requisition forms, paraffin blocks, corresponding archival slides, and histopathological reports.

Inclusion criteria: The present study included all intracranial and intraspinal meningiomas.

Exclusion criteria: Tumours of meningeal origin, such as solitary fibrous tumours, haemangiopericytoma, and haemangioblastoma, etc., inflammatory lesions of the meninges, tumours with irrelevant ancillary data were also excluded from the study.

Study Procedure

All biopsy-confirmed cases of meningioma were examined using Haematoxylin and Eosin (H&E) stained slides from the archive, which were retrieved and carefully reviewed by two pathologists within the study period (1 year). There was no grading in a few cases, so the completion of grading was done in cases with incomplete reports. In cases of missing or damaged original histopathology slides, fresh sections were taken from the tissue blocks of 5-micrometer thickness from the formalin-fixed paraffin-embedded blocks and stained with H&E stain. Histological grading of meningioma was performed according to WHO criteria [2].

For immunohistochemical analysis of PR and Ki-67, better tumour sections were used for IHC study purposes. A 3.0 µm paraffin section was placed on poly-L-lysine coated slides and was deparaffinised in xylene, followed by hydration in descending grades of ethanol. Antigen retrieval was performed by heating sections at 95ºC (3 cycles of 5 minutes each for PR and Ki-67) in citrate buffer using an antigen retrieval system (BioGenex, USA). Sections were then incubated with Power Block (Biogenex, USA) for 10 minutes to reduce non specific antibody binding, followed by incubation with primary ready-to-use monoclonal antibodies against PR (SP2 Neomarkers) and Ki-67 (Clone Ki-67, Dako) for one hour at 4ºC. After three washes with Tris-Buffered Saline (TBS), the secondary antibody was added and incubated for 30 minutes. After an additional three washes with TBS, 3,3'-diaminobenzidine substrate (DAB tetrahydrochloride) was applied to the sections for 10 minutes, and the sections were counterstained with haematoxylin, dehydrated with ethanol and xylene, and mounted permanently with DPX. In all the above immunostaining processes, counting of cells was performed in the areas where the tumour was most prominent, while areas of haemorrhage and necrosis were avoided. Lastly, the sections were stained with H&E [2].

Internal control: For PR and Ki-67, sections from known breast carcinoma stained for PR and Ki-67 were used as a positive control.

Negative control: Samples were obtained by omitting the primary antibody step during the staining procedure.

In each case, Ki-67 LI was determined by manual counting and interpreted as the number of nuclei showing positive staining (brown color) divided by the total number of nuclei, multiplied by 100% (expressed as very low, moderate, and high expression) [2]. PR expression was scored into Groups I to III as follows [2]:

Group I: Strong nuclear staining.

Group II: Moderate nuclear staining.

Group III: Very weak or absent nuclear staining.

STATISTICAL ANALYSIS

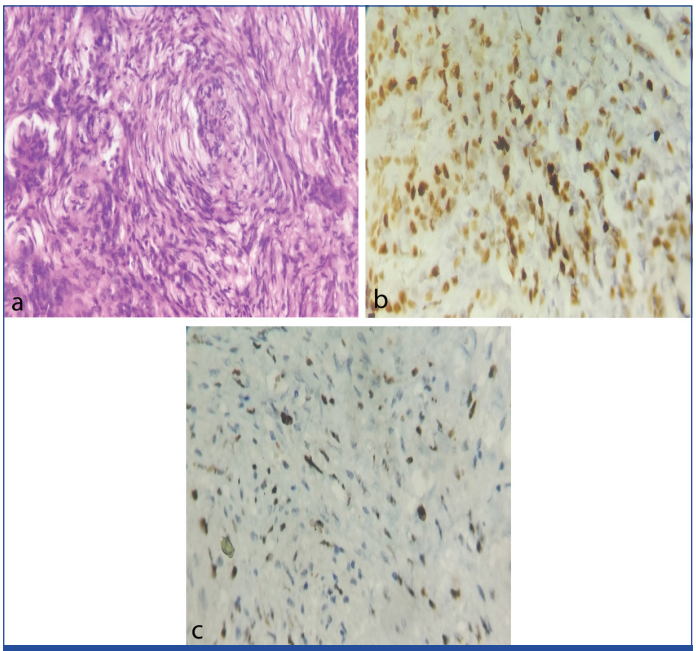
The relevant demographic data (such as age, gender, laboratory numbers, and location of the tumour) were extracted from the Departmental records and patients' folders. The data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 27.0 (IBM, Armonk, NY, USA). ANOVA and Student's t-tests were used for comparison of the means of continuous variables. The chi-square test was used for comparison of categorical variables, with a p-value of <0.05 considered significant. The obtained results were presented in tables, figures, relative frequencies, and group percentages. The correlation coefficient (Pearson's correlation coefficient) value (r-value) was measured to quantify the strength of the linear relationship between two variables (in this case, between PR and Ki-67).

RESULTS

Among the 50 cases, 30 were females, and 20 were males. The ratio of males to females was 1:1.5. The peak incidence was observed in individuals between 40 and 60 years of age (32 out of 50 cases, 64%). Total 2 women (6.66%) reported a history of using oral contraceptive pills. Only 1 (3.33%) middle-aged woman had a past history of breast cancer. None had been exposed to hormone replacement therapy. Among the male patients, 2 (10%) had undergone irradiation to the head and neck region, and 1 (5%) had a head injury in the past. The distribution of grades for the cases was as follows: Grade I- 37 (74%), Grade II- 10 (20%), and Grade III- 3 (6%). Among the Grade I tumours, meningothelial tumours were the most predominant, totaling 14 (37.83%), followed by fibroblastic tumours 9 (24.32%), transitional tumours 6 (16.21%), psammomatous tumours 4 (10.81%), angiomatous tumours 2 (5.40%), and microcystic tumours 2 (5.40%) [Table/Fig-1a].

The meningothelial variant is the most common and is characterised by a lobulated architecture, often containing whorls with indistinct cell membranes and eosinophilic cytoplasm. It features round, uniform nuclei and common intranuclear pseudoinclusions, and may have sparse psammoma bodies. The fibroblastic type generally consists of sheets of spindle cells with few or no meningothelial nests or whorls, often accompanied by thick collagen bundles. The transitional type, also known as mixed type, exhibits intermediate features between the meningothelial and fibroblastic components; whorls are well-developed, and psammoma bodies are common.

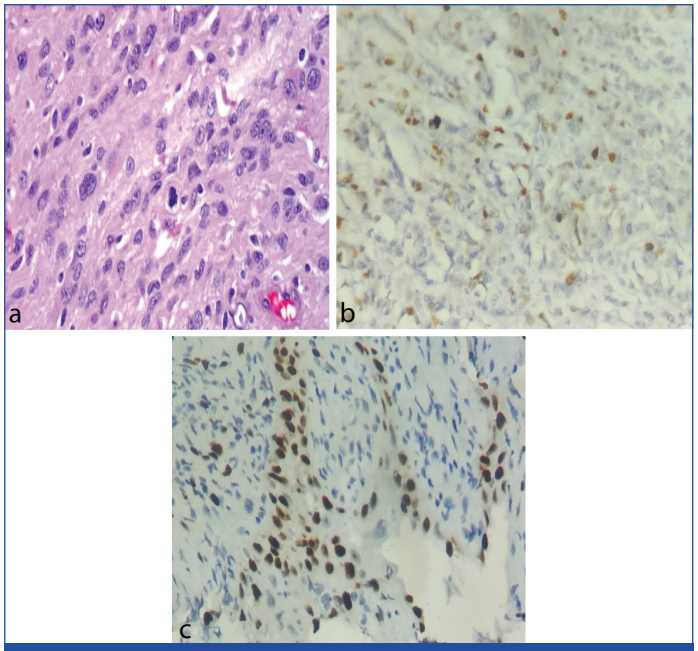
The Grade I tumours showed very strong nuclear positivity for PR and very low Ki-67 LI [Table/Fig-1b,c]. The Grade II meningiomas [Table/Fig-2a] exhibited atypical morphology with 4-19 mitotic figures per 10 high-power fields, brain invasion, or three minor criteria out of five: increased cellularity, small cell with high nuclear-cytoplasmic ratio, large prominent nucleoli, geographic necrosis, and sheet-like growth pattern (examples include clear cell type or chordoid type). The Grade II tumours demonstrated moderate nuclear intensity for both PR and Ki-67 LI [Table/Fig-2b,c]. Grade III meningioma [Table/Fig-3a] was characterised by more than 20 mitoses per 10 high-power fields or frank carcinomatous/sarcomatous histology (e.g., papillary or rhabdoid type). The Grade III tumours displayed weakly stained nuclei for PR and very high Ki-67 LI [Table/Fig-3b,c].



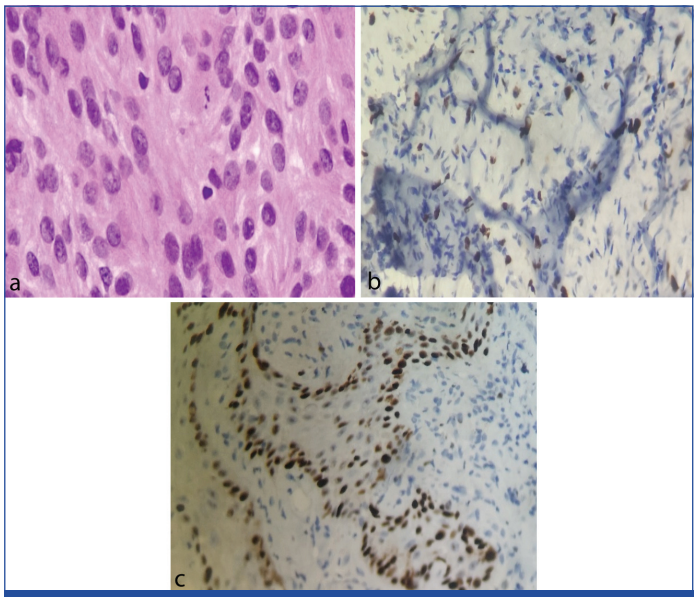
[Table/Fig-1]: a) Grade I Meningothelial meningioma (H&E, 40X); b) Progesterone Receptor (PR) status (strong nuclear positivity) (IHC, 40X); c) Very low expression of Ki-67 in the nuclei (IHC, 40X).

The PR positivity and negativity were found in 35 cases (70%) and 15 cases (30%), respectively. Among the 30 female patients, 25 exhibited positive PR staining (83.33%), whereas only 7 out of 20 male patients (35%) demonstrated PR positivity, which indicated a statistically significant gender-related difference in PR expression (p-value=0.0001) [Table/Fig-4]. A statistically significant difference in PR positivity was observed among the different grades: Grade I (26 out of 37, 70.27%, strong PR positivity), Grade II meningiomas (3 out of 10, 30%, moderate PR positivity), and the three Grade III meningiomas (PR-negative, 0 out of 3, 0%, absent to very weak PR positivity). No statistically significant association of PR was found with age (p=0.099) or histological types (p=0.056) [Table/Fig-4].

The determination of Ki-67 LIs for all 50 cases was conducted. The mean LI for male patients was 2.76% (SD=2.79%), and for female patients, it was 1.30% (SD=0.0655). This gender-related difference was statistically significant (p-value=0.002) [Table/Fig-4].



[Table/Fig-2]: a) Grade II meningioma (H&E, 40X); b) Progesterone Receptor (PR) status (moderately positive nuclei) (IHC, 40X); c) Moderate expression of Ki-67 in the nuclei (IHC, 40X).



[Table/Fig-3]: a) Grade III meningioma (H&E, 40X); b) Progesterone Receptor (PR) status (weakly stained nuclei) (IHC, 40X); c) High expression of Ki-67 in the nuclei (IHC, 40X).

The mean KI67 value was higher in Grade III meningioma (11%), whereas it was 4.16% and 6.33% in Grade I and Grade II meningiomas, respectively. This grade-related difference was statistically significant (p=0.004) [Table/Fig-4]. The mean Ki-67 value was 6.70% in PR-negative cases (n=15), with a standard deviation of 1.01. In contrast, the mean was 1.42% with a standard deviation of 5.78 in PR-positive cases (n=35).

Here, the correlation coefficient (Pearson's correlation coefficient) was measured to quantify the strength of the linear relationship between two variables (PR and Ki-67). This coefficient is symbolised by the r value, which is a unit-free value between -1 and +1. A

Different parameters	Data (number and percentage)	PR status p-value	Ki-67 status p-value
Age (years)	<40 years=15 (30%) 40-60 years=32 (64%) >60 years=03 (06%)	p=0.064 (Non significant)	p=0.81 (Non significant)
Gender	Males=20 (40.0%) Females=30 (60%)	p-value=0.0001 (Significant)	p-value=0.0002 (Significant)
Tumour site	Intracranial meningioma=42 (84%) spinal meningioma=08 (16%)	p=0.092 (Non significant)	p=0.092 (Non significant)

Histological subtypes	**Grade I tumours (n=37)** Meningothelial- 14 (37.83%) Fibroblastic- 9 (24.32%) Transitional- 6 (16.21%), Psammomatous- 4 (10.81%) Angiomatous- 2 (05.40%) Microcystic type- 2 (05.40%) **Grade II tumours (n=10)** Clear cell- 5 (50%) Chordoid- 5 (50%) **Grade III tumours (n=03)** Papillary- 2 (66.66%) Rhabdoid- 1 (33.34%)	p=0.134 (Non significant)	p=0.566 (Non significant)
Histological grade	Grade I=37 (74%) Grade II=10 (20%) Grade III=03 (06%)	p-value=0.003 (Significant)	p=0.004 (Significant)

[Table/Fig-4]: Association of different parameters with PR and Ki-67.

negative correlation was found between the Ki-67 index and PR score (R=-0.7561). This negative r value indicates a negative correlation, where the values of one variable tend to increase as the values of the other variable decrease. This means that in the case of low-grade meningiomas, there are high PR values and low Ki-67 LI values; however, in high-grade cases, this finding is reversed. The combined PR status and Ki-67 expression exhibited sensitivity and specificity of 96.67% and 100%, respectively, with an accuracy of 97.78%.

DISCUSSION

Meningioma is considered the most frequently encountered primary non glial tumour of the central nervous system [1]. In present study, the age ranged from 20 to 65 years, with the peak incidence at 45 years (mean age 47.18 years) and a male (n=20) to female (n=30) ratio of 1:1.5. In contrast, Liu N et al., reported an age range from 19 years to 85 years (N=63, M (28): F (35)=1:1.25) [3]. Mizrachi M et al., found the age range to be from 35 to 70 years, with a mean age of 46.25 years, which is similar to this study [4]. Mnango L et al., found a male to female ratio of 1:1.09 (n=67, 32 male and 35 female), with an age range from 18 months to 68 years, a mean age of 43 years, a median age of 44.6 years, and a peak age of occurrence 15-20 years earlier than present study, which is 30 years [5]. Paediatric meningiomas accounted for only 3.75% of all cases [5], and no paediatric meningioma was reported during present study period.

No significant association between age and PR status was found (p=0.064), which is similar to Liu N et al., (p=0.075) [3]. Intracranial meningiomas and spinal meningiomas accounted for 42 (84%) and 8 (16%) cases, respectively, similar to Maiuri F et al., (51 (85%) and 9 (15%)) [6]. No significant association between tumour site and PR status was found (p=0.092), which is consistent with the findings of Maiuri F et al., (p=0.072) [6]. Genetic factors, radiation exposure, hormonal alterations, and trauma are different etiological factors responsible for meningioma [6].

In this study, only one woman had a history of breast cancer. None of the patients had a history of hormone replacement therapy. Two patients had a history of irradiation to the head and neck region, and one patient had a history of head injury, which later resulted in the development of meningioma. In contrast, Maiuri F et al., reported that only two women had a past history of breast cancer, and one woman had used oral contraceptive pills [6]. None had been exposed to hormone replacement therapy.

Among the males, 2 (10%) had head injuries in the past, and 3 (15%) had undergone irradiation to the head and neck region. No significant association was found between PR and these risk factors (p=0.065) [Table/Fig-4], which is similar to the findings of Lee SH et al., (p=0.082) [7]. A study on hormonal status is essential to predict the biological behaviour (whether aggressive or not) of the tumour and also provides options for further management. Females are more prone to be affected by meningiomas due to the influence of sex steroid hormones [1].

Among the 30 female patients, 25 showed positive PR staining (83.33%), whereas only seven out of 20 male patients (35%) showed PR positivity. This gender-related difference in PR expression was statistically significant (p-value=0.0001) [Table/Fig-4]. Similarly, Lee SH et al., found that among 52 patients, 31 out of 37 female patients (83.78%) and six out of 15 male patients (40%) showed PR positivity, and this gender-related difference in PR expression was also statistically significant (p-value=0.002) [7]. This gender difference may be attributable to the higher occurrence of atypical and anaplastic meningiomas in male patients.

The PR positivity and negativity were found in 39 (65%) and 21 cases (35%), respectively. In contrast, Nagahama A et al., found slightly higher PR expression in males than females (65%), similar to findings by Mnango L et al., (62.19%) and Lee SH et al., (63.22%) [5,7,8]. Lee SH et al., did not find any significant association between PR and gender (p=0.072) [7]. PR-positive patients tend to respond best to anti-PR treatment [1].

Among the Grade I tumours, meningothelial tumours were the most predominant, accounting for 14 cases (37.83%) [Table/Fig-1a], followed by 9 (24.32%) fibroblastic tumours and 6 (16.21%) transitional type tumours. These results were similar to those of Nagahama A et al., (n=46), which found 17 meningothelial tumours (36.95%), 10 fibrous tumours (21.73%), 7 transitional tumours (15.21%), 4 psammomatous tumours (8.69%), 4 angiomatous tumours (8.69%), and 4 microcystic tumours (8.69%) [8]. Küçükosmanoğlu I et al., found predominantly transitional, fibroblastic, and syncytial meningiomas, constituting 22 (44%), 18 (36%), and 10 (20%), respectively (n=50) [8,9].

The present study found no association between histologic subtypes and PR expression (p=0.134) or Ki-67 LI (p=0.566) [Table/Fig-4], which is consistent with Küçükosmanoğlu I et al., [9] (PR expression p=0.152 and Ki-67 LI p=0.624) and Nagahama A et al., (PR expression p=0.82 and Ki-67 LI p=0.52) [8]. The expression of PR is lost as the histologic grade of the tumour increases [10]. The study by Rajeshwari B et al., was unable to demonstrate the prognostic importance of PR expression in different grades of meningiomas [10]. In this study, a significant association between tumour grades and PR expression status was observed. Lower tumour grades exhibited high PR expression, while higher tumour grades showed low PR expression.

In present study, the majority of cases were Grade I, followed by Grade II and Grade III cases: 37 (74%), 10 (20%), and 3 (6%), respectively. These findings are similar to those of Aung TM et al., {n=60; 54 (90%), 5 (8.33%), and 1 (1.66%) cases, respectively} [11]. They also carefully studied the recurrence rate and survival status in different grades of meningiomas. They reported 9 (15%) recurrent cases at the time of presentation; of these, 1 (11.11%) was spinal, and the remaining 8 (88.89%) were cranial in location. The recurrence-free survival of Grade I recurrent meningiomas was longer, i.e., 48-62 months, compared to Grade II cases, which had a survival period of 18-32 months. However, a recurrence study was not conducted by us due to time constraints.

Despite complete resection of the tumour, recurrence is not uncommon and has been estimated to occur in 10%-32% of cases [12]. Recurrence may necessitate repeat operations and can result in shortened survival [12]. A statistically significant difference in PR positivity (p-value=0.003) [Table/Fig-4] was found between Grade I (26/37, 70.27% PR positivity), Grade II meningiomas (3/10, 30% PR positivity), while all 3 Grade III meningiomas were PR-negative (0/3, 0%). Similar results were reported by Aung TM et al., who found a statistically significant difference in PR positivity (p-value=0.031) among Grade I {n=60; 40/60 (66.66% PR positivity)}, Grade II meningiomas (15/60, 25% PR positivity), and 5/60 (8.33%) Grade III meningiomas, which were PR-negative [11].

Nagahama A et al., found a significant association between PR status and increasing WHO grade (p=0.002), as well as a significant

increase in the Ki-67 proliferation index with increasing WHO grade (p=0.003) [8]. However, Bender L et al., did not identify any such significant associations (p=0.210 and p=0.223, respectively) [12]. PR positivity was found in 35 cases out of 50 (70%) and was negative in 15 cases (30%), similar to findings by Bender L et al., {n=66; 48 (72.72%) and 18 (27.28%), respectively} [12]. Umekawa M et al., found 10 positive (55.55%) and 8 negative (44.45%) PR cases among 18 analysed cases [13]. They also studied the ER status in meningioma cases (9 positive and 9 negative cases, 50% each). ER+PR+ status was detected in 77.77% (14 out of 18). No significant association between age and Ki-67 was found (p=0.81) [Table/Fig-4], which is consistent with the findings of Lee SH et al., (p=0.866) [7]. Mean LI was higher in males (2.76%) than in females (1.30%), and this gender-related difference was statistically significant (p-value=0.0002) [Table/Fig-4], similar to Nagahama A et al., (n=46). In this study, the Ki-67 index in 22 male patients was 3.84% (SD=2.86), whereas in 24 female cases, it was 2.69% (SD=0.561) (p-value=0.0002) [8]. This gender difference may suggest a higher chance of malignant meningiomas in males. Ki-67 carries significant prognostic importance, even within the same WHO category. Tumours with a higher Ki-67 index recur more frequently than those with a lower Ki-67 index within the same WHO Grade [9].

The mean Ki-67 value was higher, at 7.18% in PR-negative cases (n=15) with an SD of 4.26, while it was lower, with a mean of 3.64% and an SD of 4.17 in PR-positive cases (n=35) (p=0.0001), similar to Bender L et al., (Mean Ki-67 value was 7.87% in PR-negative cases with an SD of 4.16 and was lower, with a mean of 3.30% and an SD of 2.54 in PR-positive cases (p=0.003)) [12]. Aung Tm et al., found that a Ki-67 index of at least 5.27% was strongly associated with decreased recurrence-free survival [11].

It can be expected that tumours with a lower proliferation index will behave less aggressively than tumours with a high proliferative index (Grade II and Grade III tumours) [8]. Anaplastic carcinoma (Grade III) is recognised by abundant mitosis, necrosis, and haemorrhages; however, there can be subjective variations, making the study of Ki-67 important. Focal variability in tumour histology, grade, and chosen sections may or may not represent the most proliferative areas regarding the interpretation of Ki-67. Despite these limitations, Ki-67 can be used to assess the proliferative potential of tumours.

In present study, the values were 11%, 6.33%, and 4.16%, respectively, for Grade III, Grade II, and Grade I meningiomas, which is similar to Nagahama A et al., (n=46 cases, with values of 10.90%, 5.98%, and 4.05%, respectively) [8]. Bender L et al., (n=66) found values of 14.40%, 4.58%, and 1.48%, respectively [12]. In present study, the mean±SD of Ki-67 was 4.16±13.91, 6.33±4.77, and 11±1.732 for Grade I, Grade II, and Grade III meningiomas, respectively, and this was statistically significant with regard to grades (p=0.004) [Table/Fig-4], similar to Lee SH et al., (p=0.003) [7].

The combined sensitivity and specificity of PR status and Ki-67 expression were 96.67% and 100%, respectively, with an accuracy of 97.78%, which was quite consistent with Nagahama A et al., (95.89%, 98.87%, and 96.67%, respectively) [8]. No significant association was found between Ki-67 and the risk factors (p=0.055), similar to Aung Tm et al., (p=0.061) [11]. No significant association was found between tumour site and histological types with Ki-67 (p=0.71, p=0.56, respectively) [Table/Fig-4], similar to Lee SH et al., (p=0.75, p=0.89, respectively) [7]. An inverse correlation between PR and Ki-67 expression was demonstrated in this study (Pearson's correlation coefficient=0.7561), similar to Bender L et al., (Pearson's correlation coefficient=0.7112) and Umekawa M et al., (Pearson's correlation coefficient=0.6560) [12,13].

Limitation(s)

Despite every sincere effort, present study had some limitations, such as an inadequate sample size (only 50 cases, which seems insufficient for this kind of study). Additionally, no follow-up study was conducted to confirm recurrence cases; therefore, no IHC study was carried out for recurrent cases. The ER status was not evaluated, and no paediatric meningiomas were found during the study period. Furthermore, the study was based on a single centre and conducted in a tertiary care hospital, so the possibility of hospital bias cannot be ruled out. Lastly, a survival study was not performed.

CONCLUSION(S)

The present study shows an inverse correlation between the Ki-67 index and PR. Therefore, during the microscopic reporting of meningioma, PR and Ki-67 LI should be routinely performed to predict the chance of recurrence in a subset of patients, followed by strict follow-up of those cases, along with the benefit of more individualised treatment.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 10, 2024
- Manual Googling: Jan 04, 2025
- iThenticate Software: Jan 11, 2025 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Oct 06, 2024**
Date of Peer Review: **Dec 17, 2024**
Date of Acceptance: **Jan 14, 2025**
Date of Publishing: **May 01, 2025**