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Progesterone Receptor Expression in Relation to WHO Grade and Tumor Size in Intracranial Meningioma

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Abstract **Original Research Article**

Background: Intracranial meningioma is one of the most common primary tumors of the central nervous system. Progesterone receptor (PR) expression has been suggested as a potential marker for predicting tumor behavior. ***Objective:*** To evaluate progesterone receptor expression in intracranial meningioma in relation to WHO grade and tumor size. ***Methods:*** This cross-sectional observational study was conducted at Bangladesh Medical University (BMU), Dhaka, from June 2018 to March 2020. A total of 35 patients with histopathologically confirmed intracranial meningioma were included. Tumor size and WHO grade were recorded, and PR expression was assessed by immunohistochemistry. Data were analyzed using SPSS version 22. ***Results:*** The mean age of the patients was 59.65 ± 16.03 years, with female predominance (57.1%). Most tumors were medium sized (62.9%), and the majority were WHO grade I (88.6%). A significant association was found between PR expression and WHO grade ($p = 0.013$), with lower PR expression more common in grade II tumors. No significant association was observed between PR expression and tumor size ($p = 0.099$). ***Conclusion:*** Progesterone receptor expression shows a significant association with WHO histological grade in intracranial meningioma, suggesting its potential role as a prognostic indicator of tumor behavior. However, PR expression does not appear to correlate with tumor size.

Keywords: Intracranial meningioma, progesterone receptor, WHO grade, tumor size, immunohistochemistry.

INTRODUCTION

Intracranial meningiomas are among the most common primary tumors of the central nervous system (CNS), accounting for approximately 30–40% of all primary brain tumors in adults. These tumors originate from arachnoid cap cells of the meninges and typically exhibit slow growth and benign histological characteristics. However, despite their generally indolent nature, meningiomas may demonstrate diverse biological behavior, ranging from benign lesions with minimal clinical impact to aggressive tumors with rapid growth, recurrence, and neurological complications [1,2]. The incidence of meningioma increases with age and is significantly higher in females than in males, suggesting a possible hormonal influence on tumor development and progression [3,4].

The clinical manifestations of intracranial meningiomas depend on tumor size, location, and the degree of compression exerted on adjacent brain structures. Patients may present with symptoms such as headache, seizures, focal neurological deficits, visual disturbances, or cognitive impairment. In many cases, small meningiomas are discovered incidentally during neuroimaging performed for unrelated reasons [5] Advances in imaging techniques, particularly magnetic resonance imaging (MRI), have improved early detection and characterization of these tumors. Nevertheless, definitive diagnosis and grading rely on histopathological examination following surgical resection or biopsy [6].

The World Health Organization (WHO) classification system is widely used to categorize meningiomas based on histopathological features and predicted biological behavior [7]. According to the current WHO classification, meningiomas are divided into three grades: grade I (benign), grade II (atypical), and grade III (anaplastic or malignant) [8]. Grade I meningiomas constitute the majority of cases and generally have a favorable prognosis, whereas higher-

grade tumors demonstrate increased cellular proliferation, brain invasion, and higher recurrence rates. Accurate grading is essential because it influences treatment strategies, prognosis, and follow-up planning [9]. However, histological grading alone does not always reliably predict tumor behavior, and some grade I tumors may recur or behave aggressively. Therefore, additional molecular and immunohistochemical markers are increasingly being investigated to improve prognostic assessment [10].

Among the various biomarkers studied in meningiomas, hormone receptor expression has attracted considerable attention. Progesterone receptor (PR) expression is particularly significant due to the observed female predominance of meningiomas and reports of tumor growth during pregnancy or hormonal therapy. Studies have shown that PR expression is present in a substantial proportion of meningiomas, while estrogen receptor expression is relatively rare. The presence of PR is believed to reflect a more differentiated and less aggressive tumor phenotype, whereas loss or reduction of PR expression may indicate tumor progression and higher malignancy potential [4,6].

Several investigations have demonstrated a relationship between progesterone receptor expression and the histological grade of meningiomas [11] In general, PR positivity is more frequently observed in WHO grade I tumors compared with higher-grade lesions. For example, recent studies have reported PR expression in approximately 76.8% of grade I meningiomas, while the proportion decreases to around 61.2% in grade II and 17.3% in grade III tumors. These findings suggest that loss of PR expression is associated with increasing tumor grade and biological aggressiveness. Consequently, PR status may serve as a useful adjunct marker for predicting tumor behavior and recurrence risk [4].

Tumor size is another important clinical parameter in the evaluation of meningiomas. Larger tumors often cause greater mass effect on surrounding brain tissue and may be associated with more severe clinical symptoms [12]. Some studies suggest that larger meningiomas may demonstrate higher proliferative activity and increased likelihood of recurrence, although the relationship between tumor size and biological aggressiveness remains complex.[6] Investigating the association between tumor size and molecular markers such as PR expression may provide further insights into the biological behavior of meningiomas and help refine prognostic stratification [13]

Immunohistochemical analysis of progesterone receptor expression has therefore become an important component in the pathological evaluation of meningiomas. Combining PR status with established histopathological parameters such as WHO grade and tumor size may improve prediction of tumor behavior, recurrence risk, and patient outcomes. Understanding these relationships is essential for guiding treatment decisions, determining appropriate follow-up strategies, and identifying patients who may benefit from closer monitoring or adjuvant therapy [4,14]. Therefore, this study aims to assess progesterone receptor expression in intracranial meningiomas and to analyze its association with WHO tumor grade and tumor size as potential indicators of tumor behavior and prognosis.

Objectives

The main objective was to evaluate progesterone receptor (PR) expression in intracranial meningioma in relation to WHO grade and tumor size.

METHODOLOGY & MATERIALS

This cross-sectional observational study was conducted in the Department of Neurosurgery, Bangladesh Medical University (BMU), Shahbag, Dhaka, Bangladesh, in collaboration with the Department of Pathology. The study was carried out from June 2018 to March 2020. The study population included all patients diagnosed with intracranial meningioma who were admitted to the Department of Neurosurgery at BSMMU during the study period. The diagnosis of intracranial meningioma was initially made by contrast-enhanced magnetic resonance imaging (MRI) of the brain and was later confirmed by histopathological examination of the surgically resected tumor specimens.

Patients with radiologically diagnosed intracranial meningioma admitted to the Neurosurgery Department of BSMMU and whose diagnosis was confirmed by histopathology were included in the study. Cases in which the histopathology report was not consistent with meningioma and patients who refused to participate in the study were excluded. A structured data collection sheet, histopathology reports, and progesterone receptor immunohistochemistry reports were used as research instruments for collecting relevant information.

Prior to data collection, voluntary written informed consent was obtained from each patient or from their legal guardian after explaining the objectives and procedures of the study. At admission, a detailed history was taken and thorough general and neurological examinations were performed. The radiological diagnosis of meningioma by MRI was based on characteristic imaging features including the intensity and contrast enhancement pattern of the lesion as well as ancillary signs such as the dural tail sign and cerebrospinal fluid (CSF) cleft sign. Tumor size was measured from radiological findings and categorized as small, medium, or large based on the maximum tumor diameter.

Following surgical removal, tumor specimens were sent for histopathological examination to confirm

the diagnosis. The tumors were graded according to the World Health Organization (WHO) classification of meningioma. Immunohistochemical staining was performed to determine progesterone receptor (PR) expression in the tumor tissue, and PR status was recorded from the histopathology report.

Statistical Analysis:

Data were entered and analyzed using SPSS version 22. The results were presented in frequencies and percentages, and statistical associations between progesterone receptor expression, WHO grade, and tumor size were analyzed using the Chi-square test. A p-value of less than 0.05 was considered statistically significant. Ethical principles were maintained throughout the study, and confidentiality of patient information was strictly ensured.

RESULT

Table 1: Distribution of the study subjects according to age and sex (N = 35)

Variable	Male n (%)	Female n (%)
≤30	2 (13.3)	4 (20.0)
31–40	2 (13.3)	5 (25.0)
41–50	2 (13.3)	2 (10.0)
51–60	6 (40.0)	5 (25.0)
61–70	3 (20.0)	2 (10.0)
>70	0 (0.0)	2 (10.0)
Mean ± SD	59.65 ± 16.03	
Range	17–82 years	

Table 1 shows the age and sex distribution of the study subjects. Among the 35 patients, 15 (42.9%) were male and 20 (57.1%) were female. The age of the patients ranged from 17 to 82 years with a mean ± SD of 59.65 ± 16.03 years. The highest proportion of patients was observed in the 51–60 years age group. Female predominance was noted in most age groups, particularly in the 31–40 years group.

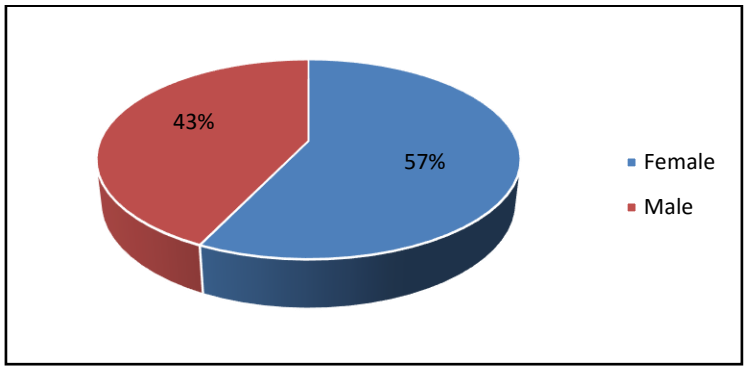

Figure 1: Gender distribution of the study population

Figure 1 shows the gender distribution of the study population. Among the 35 patients, 20 (57.1%) were female and 15 (42.9%) were male, indicating a female predominance.

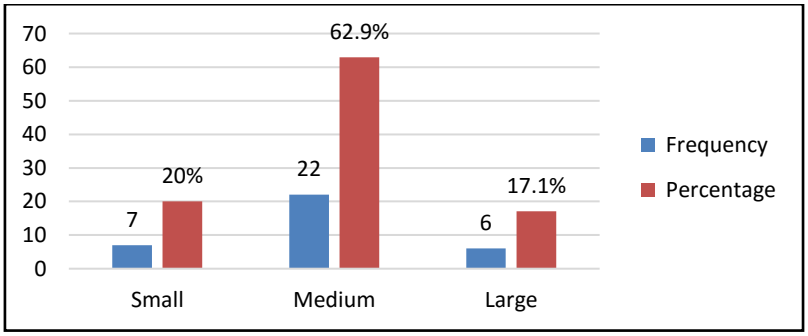

Figure 2: Distribution of intracranial meningioma according to tumor size (N = 35)

Figure 2 shows the distribution of tumor size. Most tumors were medium-sized 22 (62.9%), followed by small tumors 7 (20.0%) and large tumors 6 (17.1%).

Table 2: Distribution of intracranial meningioma according to WHO grade (N = 35)

WHO Grade	Frequency (n)	Percentage (%)
Grade I	31	88.6
Grade II	4	11.4
Grade III	0	0

Table 2 demonstrates the histopathological grading of meningioma. The majority of tumors were WHO Grade I (88.6%), while 11.4% were Grade II, and no Grade III tumor was found.

Table 3: Association between progesterone receptor expression and WHO grade of meningioma (N = 35)

PR Expression	WHO Grade I (n=31)	WHO Grade II (n=4)	Total	p-value
Absent	0	0	**0**	0.013
<10%	3 (9.7%)	3 (75.0%)	6	
10–50%	19 (61.3%)	1 (25.0%)	20	
51–80%	9 (29.0%)	0 (0.0%)	9	
>80%	0	0	0	
Total	31	4	35	

Statistical Test: Fisher's Exact Test

Interpretation: A statistically significant association was observed between progesterone receptor status and histopathological grading (p = 0.013).

Table 3 shows the association between progesterone receptor (PR) expression and WHO grade of meningioma. Lower PR expression was more common in Grade II tumors, while higher PR expression was predominantly observed in Grade I tumors. This association was statistically significant (p = 0.013).

Table 4: Association Between Progesterone Receptor expression and Tumor Size

PR Expression	Small (n=7)	Medium (n=22)	Large (n=6)	Total	p-value
Absent	0	0	0	0	0.099
<10%	0	6	0	6	
10–50%	4	10	6	20	
51–80%	3	6	0	9	
>80%	0	0	0	0	
Total	7	22	6	35	

Statistical Test: Fisher's Exact Test

Interpretation: No statistically significant association was found between progesterone receptor status and tumor size (p > 0.05).

Table 4 presents the association between progesterone receptor expression and tumor size. Most tumors with PR expression 10–50% were seen across all tumor sizes. However, no statistically significant association was observed between PR expression and tumor size (p = 0.099).

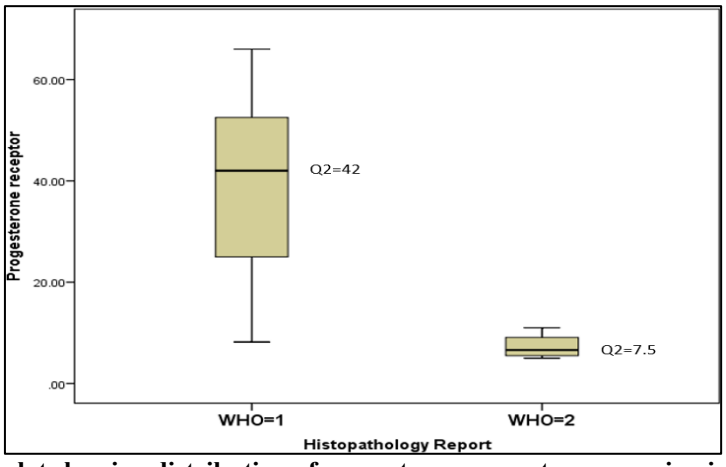

Figure 3: Box plot showing distribution of progesterone receptor expression in WHO grades

Figure 3 shows the box-plot distribution of progesterone receptor (PR) expression according to WHO grade of meningioma. The median PR expression was 42% in WHO Grade I tumors and 7.5% in WHO Grade II tumors.

DISCUSSION

Intracranial meningioma is one of the most common primary tumors of the central nervous system and is generally considered a benign and surgically curable lesion. However, recurrence remains a significant concern, even after apparently complete resection. Previous studies have reported recurrence rates ranging from 10% to 32%, even after total tumor removal [15]. The most obvious reason for recurrence is incomplete surgical excision; however, recurrence has also been observed in cases where tumors were macroscopically totally removed according to Simpson grade I criteria. Some studies reported recurrence rates of 4–15% even after complete resection, indicating that additional biological factors may influence tumor behavior [16]. The biological behavior of meningioma is highly variable, and conventional prognostic factors such as WHO histological grading and Simpson grading of tumor resection do not always accurately predict tumor growth and recurrence. Therefore, evaluation of molecular and hormonal markers has been suggested to better understand tumor biology and predict clinical outcomes. Hormonal receptor status, particularly progesterone receptor (PR) expression, has been investigated as a potential prognostic indicator in meningioma [17] Several studies have shown that sex hormone receptors influence tumor prognosis. Meningiomas expressing progesterone receptors generally demonstrate more favorable biological behavior and lower recurrence rates compared with tumors lacking hormone receptors. Tumors with positive progesterone receptor expression show recurrence rates around 5%, whereas tumors lacking hormone receptors may demonstrate recurrence rates as high as 30% [18]. Nevertheless, WHO tumor grade remains one of the most important prognostic factors, with reported relapse rates of approximately 7% for grade I, 40% for grade II, and up to 80% for grade III meningiomas [19] Although most grade I meningiomas are considered benign, late recurrences may occur even after long periods of follow-up, sometimes exceeding 20 years [20] The presence of hormone receptors in meningioma has been studied extensively since the first report by Donnell *et al.,*in 1979 [21] Early studies mainly used receptor-binding assays to detect estrogen and progesterone receptors, but these methods produced inconsistent results due to technical limitations and differences in tissue handling [21,22]. With the development of monoclonal antibodies, immunohistochemical techniques have become widely used to evaluate hormone receptor expression in meningiomas. Immunohistochemistry provides a reliable and rapid method for detecting receptor status directly in tumor tissues and allows retrospective analysis using archived specimens [23,24]. Previous studies have demonstrated an inverse relationship between progesterone receptor expression and tumor grade. Roser *et al.,*(2004) reported significantly higher PR expression in benign meningiomas compared with atypical or anaplastic tumors [17] Similarly, Cahill *et al.,*(1984) and Brandis *et al.,*(1993) reported lower progesterone receptor expression in higher-grade meningiomas [22,25] PR-negative tumors have also been shown to exhibit more aggressive biological behavior than PR-positive tumors [26] Furthermore, Maiuri *et al.,*(2007) suggested that progesterone receptor negativity may predict recurrence even in histologically benign meningiomas [27] In the present study, the majority of tumors were WHO grade I meningiomas (88.6%), while 11.4% were WHO grade II tumors, and no grade III tumors were observed. The absence of malignant meningiomas in the present study may be related to the relatively small sample size and the short study duration, as anaplastic meningiomas are relatively rare. These findings are consistent with previous reports indicating that approximately 80% of meningiomas are WHO grade I tumors, whereas grade II and grade III tumors account for 15–20% and 1–3% of cases, respectively [28,29] Our results demonstrated a significant association between progesterone receptor expression and histopathological grading of meningioma. Among the 31 grade I tumors, the majority showed moderate PR expression (10–50%), while a smaller proportion demonstrated higher expression (51–80%). In contrast, most grade II tumors showed low PR expression (<10%). Statistical analysis using Fisher's exact test revealed a significant association between progesterone receptor expression and tumor grade ($p = 0.013$). These findings support the hypothesis that PR expression decreases with increasing tumor grade. Similar results were reported by Shayanfar *et al.,*(2010), Maiuri *et al.,*(2007), Roser *et al.,*(2004), Cahill *et al.,*(1984), and Brandis *et al.,*(1993) [17, 22, 23, 25, 30] The present study also demonstrated that progesterone receptor expression tended to be higher in female patients compared with males. This observation is consistent with previous reports suggesting that hormonal factors may play a role in the pathogenesis of meningioma [30] However, some investigators have reported that progesterone receptor expression is not significantly associated with patient age, sex, tumor location, or tumor size [31,32] In the present study, tumor size distribution showed that the majority of tumors were medium-sized (62.9%), followed by small tumors (20.0%) and large tumors (17.1%). However, statistical analysis showed no significant association between progesterone receptor expression and tumor size ($p = 0.099$). These findings are consistent with previous studies by Fewings *et al.,*(2000) and Ironside *et al.,*(1986), which also reported no correlation between hormone receptor expression and tumor size [31,32] Clinically, meningiomas often present with symptoms related to mass effect or compression of adjacent neural structures. Previous studies have reported common presenting symptoms including headache, seizures, visual disturbances, cranial nerve deficits, and focal

neurological deficits [28,33] In the present study, the most common presenting symptom was headache (91.4%), followed by dimness of vision (45.7%), convulsions (37.1%), and vomiting (31.4%). These findings are consistent with previously reported clinical presentations. Regarding tumor location, meningiomas most frequently occur in the parasagittal region, convexity, sphenoid ridge, and tuberculum sellae, while less common sites include the falx, tentorium, and cerebellopontine angle [20] In the present study, the most common location was the parasagittal region (28.6%), followed by convexity (25.7%) and sphenoid ridge (17.1%), which is comparable to findings reported by Magill *et al.,*(2018) [28] The demographic characteristics of our study population were also consistent with previous literature. Meningiomas are known to occur most commonly in the fifth and sixth decades of life, with a higher prevalence among females [34,35] In the present study, the mean age was 59.65 ± 16.03 years, and the majority of patients were between 51 and 60 years of age. Females constituted 57.1% of the study population, with a male-to-female ratio of 1:1.33. Similar demographic patterns have been reported in previous studies by Mukherjee *et al.,*(2011) and Magill *et al.,*(2018) [28,36] Overall, the findings of the present study support the concept that progesterone receptor expression is associated with histopathological grade of meningioma, with lower receptor expression observed in higher-grade tumors. However, no significant relationship was observed between progesterone receptor expression and tumor size. These results suggest that progesterone receptor expression may serve as a useful prognostic biomarker for predicting the biological behavior of intracranial meningiomas.

Limitations of the study

This study had a small sample size (n = 35) and was conducted in a single center, which may limit generalizability. No WHO grade III meningioma cases were included due to their rarity. In addition, long-term follow-up and other molecular markers were not evaluated.

CONCLUSION

This study demonstrates that progesterone receptor expression is significantly associated with the WHO histopathological grade of intracranial meningioma, with higher expression observed in lower-grade tumors. However, no significant association was found between progesterone receptor expression and tumor size. These findings suggest that progesterone receptor status may serve as a useful prognostic marker for assessing the biological behavior of intracranial meningiomas.

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Conflicts of interest: There are no conflicts of interest.

Ethical approval: The study was approved by the Institutional Ethics Committee.

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