

Original Article

# Correlation of progesterone receptors and P63 to the histological grade of meningiomas: Review and significance in an African population

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## ABSTRACT

**Objectives:** Meningiomas, a common neoplasm of the central nervous system, is a widely studied meningeal tumor. According to the World Health Organization (WHO) 2021 classification of meningiomas, there are 15 subtypes that have been grouped into grades 1, 2, and 3. The WHO grade 1 meningiomas are generally grouped as benign while the WHO grades 2 and 3 tumors are grouped as malignant. Progesterone receptors and P63 are common immunohistochemical markers that have proven useful in the diagnosis, grading, and prognostication of many neoplasms such as breast carcinoma, prostate carcinoma, and gastrointestinal tumors in histopathology practice. The application of these immunohistochemical markers to the grading of meningiomas has been reported and their usefulness documented in reports from Africa, Europe, North America, South America, and Asia. This study, therefore, seeks to determine if these findings are applicable to the meningiomas seen in an African population.

**Materials and Methods:** A 10-year review of results and histologically diagnosed cases of meningiomas received in the Department of Morbid Anatomy, University of Nigeria, Enugu. Immunostaining for progesterone receptors (PgRs) and P63 were done and results compared with histologic grades.

**Results:** The three WHO grades of meningioma were assessed in this study. M: F ratio was 1:1.4 and peak age was 41–50 years age range (SD ± 16.54). The majority of the cases were WHO grade 1 (86.1%) while the WHO grades 2 and 3 tumors were 8% and 5.9%, respectively. The fibrous variant was the most common subtype (27.1%). There was no correlation between progesterone receptor and P63 immunopositivity to the WHO grades of meningioma ( $P = 0.112$  and  $P = 0.138$ , respectively).

**Conclusion:** Our study showed that progesterone receptors and P63 immunopositivity did not correlate with the WHO grades of meningiomas. This may be due to the predominant variant of meningioma seen in this study. These findings indicate that PgR antagonist may not be an effective alternative for treatment in patients with inoperable meningiomas. Furthermore, P63 immunopositivity may not be a sufficient grading tool for managing meningiomas in our population.

**Keywords:** Meningioma, Progesterone receptors, P63, Africa, Central nervous system tumors

## INTRODUCTION

Meningioma is a commonly diagnosed brain tumor in Nigerian adults.<sup>[1,2]</sup> They arise from the meningeal arachnoid cells and they exert pressure as a result of growing in enclosed spaces with negligible flexibility. They are mostly benign slow-growing tumors. About 80% of meningiomas are benign. The rest have been classified as atypical (~17%) and anaplastic (~2%) due to their aggressive clinical behavior.<sup>[3]</sup>

Immunohistochemistry is important in the diagnosis and management of meningiomas. A study by Boulagon-Rombi

*et al.*<sup>[4]</sup> reported that progesterone receptors showed a decreasing percentage of positivity with increasing the World Health Organization (WHO) grade. P63 immunopositivity in meningiomas has been explored in the grading of meningiomas. Sharifi and Katebi reported 83.2% immunopositivity in the WHO grade 1 tumors and 100% immunopositivity in the WHO grades 2 and 3 tumors.<sup>[5]</sup>

Progesterone is an endogenous steroid hormone mostly produced by the corpus luteum in the ovaries. The central nervous system expresses PgRs where progesterone exerts regulation of cell function and neuroprotective function.<sup>[6]</sup> A

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study comparing progesterone receptor immunostaining in normal meninges and meningioma tissue reported 60.3% and 47.4% positivity, respectively,<sup>[7]</sup> indicating a reduction in PgRs expression in neoplastic meningeal tissue. Progesterone receptors are transcription factors with two documented isoforms, progesterone receptor A (PRA) and progesterone receptor B (PRB). When unbound to progestins, they are located in the cytoplasm, bound to heat shock proteins. When bound to progestins, they are unbound from the heat shock proteins, undergo structural reconfiguration and nuclear migration.

P63 is a protein product of the transformation-related protein 63 gene in the family of p53 gene. It is a nuclear protein with two known isoforms. The P63 with transactivation domain (TAP63) variant is differentially expressed in the brain.<sup>[8]</sup> TAP63 has been implicated in heart development and premature aging.<sup>[9,10]</sup>

Limited data are available on immunostaining of PgRs and P63 in meningiomas in Nigeria. A significant expression of PgRs in different grades of meningiomas varies widely in many studies. This validates the need for further studies of meningiomas in our environment. The evaluation of PgRs and P63 and the correlation to the WHO histological grades of meningiomas in our environment would provide baseline data on the tumor biology, immunohistochemical patterns, and possibility of chemotherapy use for management.

## MATERIALS AND METHODS

This study was a 10-year retrospective study of 107 cases of histologically diagnosed meningiomas. One hundred and thirty formalin-fixed paraffin-embedded tissue blocks of meningiomas were reviewed by two pathologists and the WHO grades as defined by the 2021 WHO classification for meningiomas were assigned according to their histological features. The exclusion criteria included cases in which the tissue blocks were missing, damaged, or exhausted and cases with incomplete clinical information.

Immunohistochemical studies with anti-progesterone receptors (PgRs) antibodies (Clone: Monoclonal, Source: Invitrogen, USA, Batch No. PA5-82163) and anti-P63 antibodies (Clone: Polyclonal, prediluted, Source: Invitrogen, USA, Batch No PA5-36069), and Ultra-Sensitive ABC Peroxidase Staining Kit (Source: ThermoScientific™, USA, Batch No. 32052) were used to stain fresh 4 micrometer sections from formalin-fixed paraffin-embedded tissue blocks.

The histologically diagnosed cases of meningioma were classified into the WHO grades based on their morphology on H and E staining. The histological and immunohistochemical aspects of this study were carried out in the histopathology laboratory of the Department of Morbid Anatomy, UNTH, Enugu.

The “2010 ASCO/CAP Guideline Recommendations for Immunohistochemical (IHC) Testing of estrogen receptors

and PgR in Breast Cancer” was adapted for interpretation of anti-progesterone and anti-p63 immunostains where brown nuclear staining only was interpreted as positive and blue nuclear staining were interpreted as negative. Progesterone receptors and P63 were interpreted semi-quantitatively using only a percentage of positive tumor cells, no staining indicating absence of positive tumor cells, mild staining indicating 1–10% of positive staining nuclei, moderate staining indicating 11–50% of positive staining nuclei, and intense staining indicating 51–100% of positive staining nuclei.

The data obtained were tabulated using 2016 Microsoft Excel and subsequently analyzed using IBM, SPSS 22 statistical package. Chi-square test was used for the comparison of discontinuous variables with  $P < 0.05$  considered as significant and Kendall's Tau-b coefficient was used to confirm  $P$ -value.

All procedures performed in this study were approved by the University of Nigeria Teaching Hospital IRB (NHREC/05/01/2008B-FWA00002458-IRB00002323; February 12, 2020) in accordance with the 1964 Helsinki Declaration and its later amendments.

## RESULTS

One hundred and seven meningiomas met the inclusion criteria in our study. Sixty-two occurred in females and 45 occurred in males giving a female-to-male ratio of 1.4:1. The ages ranged from 6 years to 88 years (SD  $\pm$  16.54). The peak age was in the 41–50 years (SD  $\pm$  16.54) age group (23.4%) and was closely followed by a 19.6% prevalence in the 51–60 years (SD  $\pm$  16.54) age group. Fibrous, meningothelial, and psammomatous meningiomas were the most common variants seen in this study with 27.1% (29 cases), 21.5% (23 cases), and 19.6% (17 cases), respectively.

The overall immunohistochemical staining pattern is presented in Table 1. Progesterone receptor staining was highest in the WHO grade 1 tumors compared to other grades while P63 was highest in WHO grade 2 tumors, also reported in Table 1. The statistical relationship between the WHO grade and the immune stains is shown in Table 2. The PgR and P63 staining is shown in Figures 1 and 2, respectively.

## DISCUSSION

For the immunostains, progesterone receptors and P63 showed an average of 45.5% and 30.8% positivity, respectively, across the three WHO grades that were studied. The immunopositivity of progesterone receptors showed an inverse correlation to the WHO grades; grade 1 (39.4%), grade 2 (25%), and grade 3 (0%). Progesterone is an endogenous steroid hormone involved in reproduction

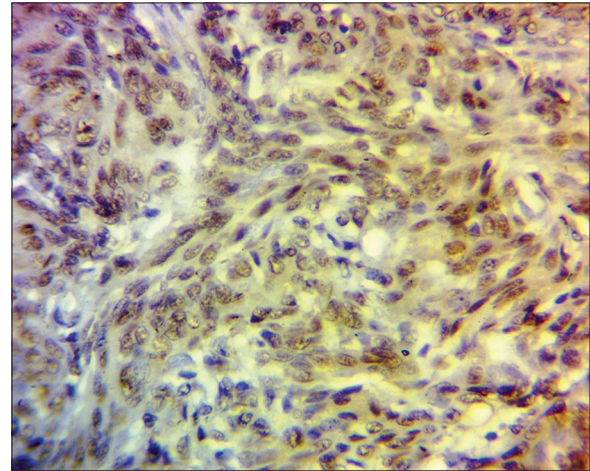
**Table 1:** Distribution and relationship of progesterone receptor and P63 to the WHO grades.

Variables	Grade 1 (n=94)	Grade 2 (n=8)	Grade 3 (n=5)
	n (%)	n (%)	n (%)
Progesterone receptor			
No staining	57(60.6)	6(75.0)	5(100.0)
Mild	20(21.3)	1(12.5)	0(0.0)
Moderate	16(17.0)	0(0.0)	0(0.0)
Intense	1(1.1)	1(12.5)	0(0.0)
		(P=0.112)	
P63			
No staining	68(72.3)	3(37.5)	3(60.0)
Mild	13(13.8)	2(25.0)	0(0.0)
Moderate	7(7.4)	1(12.5)	0(0.0)
Intense	6(6.4)	2(25.0)	2(40.0)
		(P=0.138)	

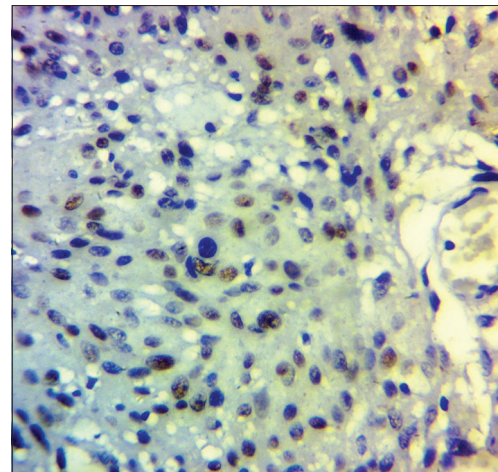
**Table 2:** Relationship between variables.

Diagnosis/Type	Kendall's Tau-b	P-value
Grade PR	0.118	0.112
Grade P63	0.195	0.138

and embryogenesis. It also plays an important role as a neurosteroid where it interacts with non-nuclear PgRs and sigma receptors to act as neuromodulators. In this study, there was no statistical significance between PgR immunostaining and the WHO grades of meningioma. The reduced progesterone receptor immunoreactivity in this study may be due to the prevalent type of the WHO grade 1 meningioma found in this study (fibrous variant). This finding is partly supported by the study done by Omulecka *et al.*<sup>[11]</sup> where 64 meningioma samples were studied with 21 transitional and 13 fibrous variants. They reported a 42.2% immunopositivity in fibrous meningioma as against 100% immunopositivity in meningothelial meningioma. There are varying reports on PgR immunoreactivity and the WHO grades of meningioma in the literature. Ikeri *et al.*,<sup>[12]</sup> in their study in Lagos, Nigeria, reviewed 72 meningioma cases in their study and they found an inverse correlation between the WHO grades and the progesterone receptor expression. However, more cases were investigated in our study and the common subtypes were at variance with the findings from Lagos, Nigeria. Csonka *et al.*<sup>[13]</sup> and Wolfsberger *et al.*<sup>[14]</sup> both found an inverse relationship between the WHO grade of meningioma and PgR positivity in their studies, Perrot-Appanat *et al.*<sup>[15]</sup> and Ceylan and Ozmen.<sup>[16]</sup> both reported a weak inverse correlation. A systematic review by Agopiantz *et al.*<sup>[17]</sup> showed that 72.2% of meningiomas expressed



**Figure 1:** Photomicrograph shows intense progesterone receptor immunopositivity in a World Health Organization grade 1 meningothelial meningioma.



**Figure 2:** Photomicrograph shows P63 immunopositivity in the World Health Organization grade 2 atypical meningioma.

PgRs; however, the majority of the articles that were reviewed were not studies done on the indigenous African population, thus raising the possibility of varying expression of PgR expression in the meningiomas seen in the African population.

P63 immunoreactivity showed positive staining in 27.6% of the WHO grade 1 tumors, 62.5% of the WHO grade 2 tumors, and 40% of the WHO grade 3 tumors. This was not statistically significant ( $P = 0.138$ ). Reports from studies conducted in Iran, India, and USA have shown increasing immunopositivity of P63 with increasing WHO grades of meningiomas.<sup>[5,18,19]</sup> In this study; however, a significant percentage of the WHO grade 1 tumors showed immunopositivity (27.6%) similar to the report by Mittal *et al.*<sup>[20]</sup> in India where their study showed 34.9% immunopositivity in the WHO grade 1 tumors thus

concluding that it cannot be used as a sole marker in grading meningiomas.

In our study, we found a poor correlation between PgRs and P63 with the WHO grade of meningioma. Due to the poor expression of progesterone receptors, the use of anti-progestins as an alternative chemotherapeutic agent may not be beneficial to patients in our environment.

## CONCLUSION

Contrary to many other study findings, this study did not show any correlation between progesterone receptors and P63 with the WHO grades of meningioma. This may be due to varying degree of expression of progesterone receptors and P63 in different variants. Thus, we concluded in this study that progesterone receptors and P63 immunostains may not be beneficial for grading meningiomas in cases submitted for histopathological assessment.

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## Ethical approval

All procedures performed in this study were approved by the University of Nigeria Teaching Hospital IRB (NHREC/05/01/2008B-FWA00002458-IRB00002323; February 12, 2020) in accordance with the 1964 Helsinki Declaration and its later amendments.

## Declaration of patient consent

The Institutional Review Board (IRB) permission obtained for the study.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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