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Original Article

Prognostic importance of progesterone receptor expression in meningioma

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Abstract

Aim: : In this study, our objective was to demonstrate the relationship of progesterone receptor (PR) expression with histological grade and other prognostic factors in patients with meningiomas.

Material and Methods: Brain biopsy materials, which were examined and diagnosed with meningioma between January 2011 and January 2015, were screened in a retrospective study design. Ninety-six of the cases, who were diagnosed with meningioma with a grade of I, II, and III according to WHO and had undergone immunohistochemically PR expression, were included in the study.

Results: JThere was a weak correlation between WHO grade and PR expression rate and intensity in our study. PR expression rate and intensity showed increment as the grade progressed. On the other hand, there was no correlation of PR expression rate and intensity with other prognostic parameters such as Ki67 proliferation index and mitotic index.

Conclusion: Although we have detected a weak correlation between PR expression rate and intensity with WHO grade, we think that PR expression rate and intensity do not have prognostic role in the meningiomas due to the absence of a similar relationship between other important parameters in prognosis. In most of the studies in the literature, it is reported that PR expression rate and intensity decreases with increasing WHO grade. However, the number of studies with the opposite results is high. In the presence of conflicting data in the literature and considering that almost all of these studies were performed according to the WHO classification before 2016 (before the new WHO classification), we concluded that further multi-centre studies utilizing new classification system and have more homogeneous distribution of the grades are required to investigate the relationship between PR and histopathologic grade and other prognostic parameters.

Keywords: Meningioma; progesterone receptor; prognostic factors

INTRODUCTION

Meningiomas originate from the meningothelial cells and are usually benign tumors with slow growth. They constitute 33.8% of all primary brain tumors (1,2). They are usually encountered in elderly females (3). Although the majority of meningiomas have a benign character, there are also atypical and anaplastic types, which lead to increased morbidity and mortality due to their poor prognosis. Prognosis is depend on the histological grade, histological subtype, and proliferation grade (2).

The histological grading of WHO (World Health Organization) is critical for the prognosis and the therapy and is the most important prognostic parameter. While atypical meningioma (WHO Grade II) had been diagnosed with the detection of (10 HPF) 4-19 mitosis and/or at least 3 of 5 atypical features (prominent nucleoli, loss of pattern, hypercellularity, small cell change, necrosis) in a 10x magnification field and/or presence of chordoid, clear-cell pattern until 2016, brain invasion was included in this category after 2016 WHO classification (4, 5). Observation of the rhabdoid or papillary pattern, 20 or more mitosis in 10 HPF, prominent carcinomatous or sarcomatous growth leads to the diagnosis of WHO Grade III meningioma (5). Although a more aggressive course along with relapses is encountered in cases with WHO Grade I meningioma, interestingly a high survival rate and slow progression are observed in cases with WHO Grade II and WHO Grade III. Therefore, in recent years other factors independent from the aggressive course and WHO grading are under

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research and the relationship between hormone receptors and prognostic factors, which are considered to have an important role in tumorigenesis, are explored (6).

It is believed that the hormonal stimulation is important for tumorigenesis and growth because of the aggravation of the symptoms during pregnancy and the luteal phase of the menstrual cycle and concomitant occurrence of breast cancer. From this point of view, progesterone receptor (PR) is an important marker. There are several studies focused on this topic (7). However, the studies in the literature demonstrating the relationship of the PR expression with the histological grade and prognosis presented conflicting results. In our study, we aimed to investigate the relationship between the PR expression rate, intensity of staining, age, sex and Ki67 proliferation index and WHO grade according to the 2016 classification, which is one of the important prognostic parameters.

MATERIAL and METHODS

Ninety-six of 117 patients diagnosed with WHO Grade I-III meningioma between January 2013 and January 2014, who had undergone PR expression analysis, were included in the study. The brain biopsy materials of the included patients were retrospectively investigated. Four micron-thick sections were obtained from the blocks containing the most intensive tumor tissue and placed on the charged glass slides, which were kept in an incubator at 70°C for 15 minutes. Then the slides were placed in the automated immunohistochemistry staining platform (Ventana, Roche, USA). After the slides went through deparaffinization and dehydration processes respectively, they were processed in the device with ULTRA Cell Conditioning Solution, hydrogen peroxidase, PR antibodies (Nova Castra, Leica, Newcastle, United Kingdom).

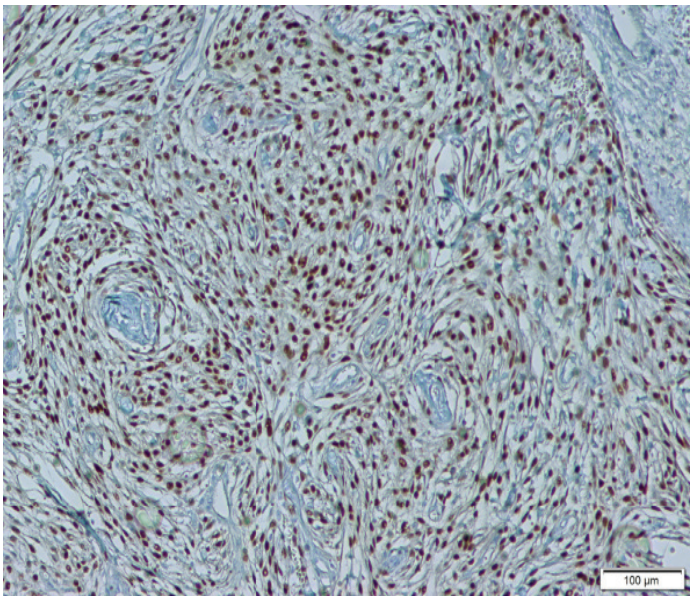

Figure 1. Grade 3 PR staining rate (positive staining of 51%-100% of tumor cells) and staining intensity (strong nucleus staining)

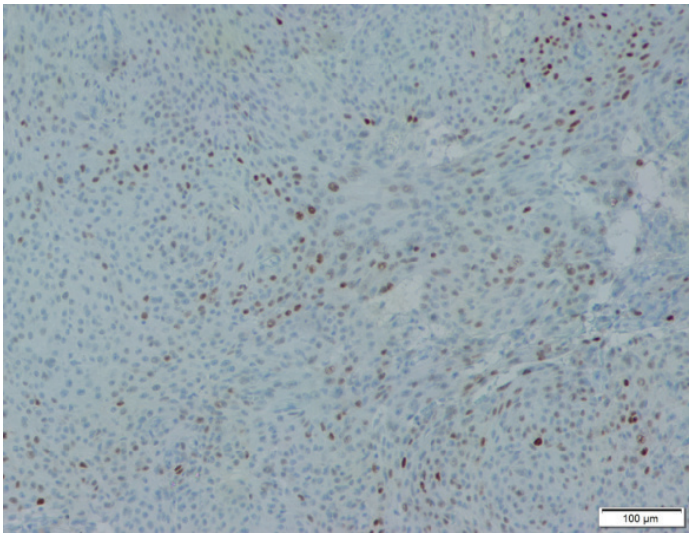

Figure 2. Grade 2 PR staining rate (positive staining of %11-50 of tumor cells) and staining intensity (moderate nucleus staining)

The staining pattern for PR staining rate was defined as follows: (0) negative staining; (1) positive staining of 1%-10% of tumor cells; (2) positive staining of 11%-50% of tumor cells; (3) positive staining of 51%-100% of tumor cells (Figure 1, 2, 3) (8).

The staining pattern for PR staining intensity was defined as follows: (0) negative staining; (1) weak nucleus staining; (2) moderate nucleus staining; (3) strong nucleus staining (Figure 1, 2, 3) (8).

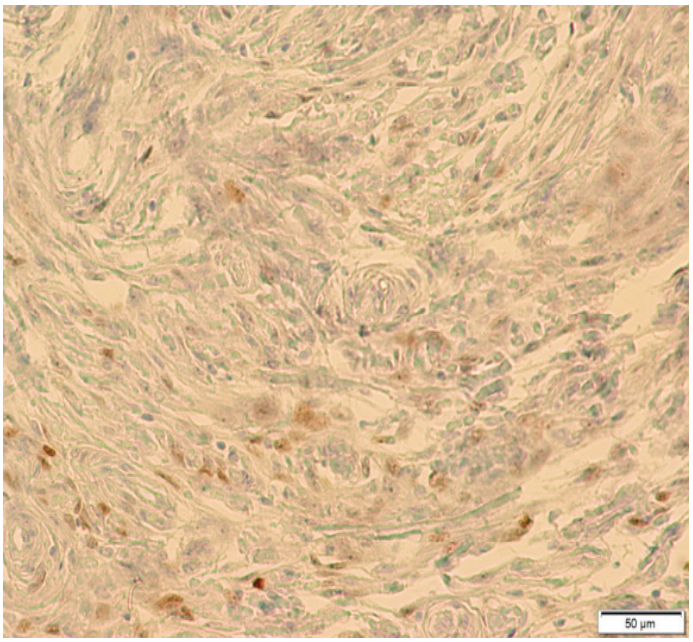

Figure 3. Grade 1 PR staining rate (positive staining of %1-10 of tumor cells) and staining intensity (weak nucleus staining)

Mitotic activity was classified as follows: grade 1: 0-3 mitosis in 10 BBA, grade 2: 4-19 mitosis in 10 BBA, grade 3: ≥ 20 mitosis in 10 BBA (8).

Table 1. The relationship between PR staining rate, staining intensity and WHO grade

	Marker Grade (n)	WHO Grade 1 (n:53)		WHO Grade 2 (n:38)		WHO Grade 3 (n:5)		P Value
		No	%	No	%	No	%	
PR staining rate	0 (9)	7	%13	2	%5	0	%0	p: 0.028
	1 (22)	18	%34	3	%8	1	%20	
	2 (25)	9	%17	14	%37	2	%40	
	3 (40)	19	%36	19	%50	2	%40	
PR staining intensity	0 (9)	7	%13	2	%5	0	%0	p: 0.002
	1 (24)	19	%36	4	%11	1	%20	
	2 (31)	15	%28	14	%37	2	%40	
	3 (32)	12	%23	18	%47	2	%40	

The Ki67 proliferation index was classified as follows: grade 1: % 0-10 of tumor cells, grade 2: % 11-50 of tumor cells; grade 3: % 51-100 of tumor cells. The relationship of PR staining rate and intensity with the age, gender, histological grade, Ki67 proliferation index, and mitotic activity (8).

The study was approved by the Local Ethics Committee (B.30.2.ATA.0.1.00/543).

Statistical Analysis

D'Agostino Pearson test was used to determine whether the data fit the normal distribution. Normally distributed binary data groups were compared using independent t test. The Chi square test was used to compare the ordered variables. Pearson correlation was used for correlations between ordered variables. The test was accepted as significant when two-tailed p values were <0.05. Statistical analyses were performed using the Medcalc program (Medcalc ver 16. Ostend, Belgium).

RESULTS

The mean age of the 96 participants was 55.9±11 years (females: 54.2±11.5, males: 58.8±9.7). There was no significant difference between females and males for the age (p: 0.052). Sixty-two of the cases were female (F/M ratio: 1.8/1).

Eighty-seven (90.6%) of the cases were PR positive. There was no statistically significant difference between the age and PR positivity (p=0.783). There was also no statistically significant difference between the genders for PR positivity (p=0.821). The rate of PR positivity was 92.1% and 88.3% in males and females respectively.

Table 2. The relationship between PR staining rate, staining intensity and Ki67 proliferation index, mitotic activity and brain invasion

	Marker Grade (n)	Ki67 Proliferation Index Grade (n)			Mitotic Activity Grade (n)			Brain invasion (n:40)
		1 (61)	2 (29)	3 (6)	1 (79)	2 (13)	3 (4)	
PR staining rate	0 (9)	8 (%13)	1 (%3)	0 (%0)	8 (%10)	1 (%8)	0 (%0)	1 (%3)
	1 (22)	11 (%18)	9 (%31)	2 (%33)	20 (%25)	0 (%0)	2 (%50)	4 (%10)
	2 (25)	19 (%31)	6 (%21)	0 (%0)	19 (%24)	6 (%46)	0 (%0)	15 (%37)
	3 (40)	23 (%38)	13 (%45)	4 (%67)	32 (%41)	6 (%46)	2 (%50)	20 (%50)
P Value		**p: 0.344**				**p: 0.327**		**p: 0.037**
PR staining intensity	0 (9)	8 (%13)	1 (%3)	0 (%0)	8 (%10)	1 (%8)	0 (%0)	1 (%3)
	1 (24)	11 (%18)	11 (%38)	2 (%33)	21 (%27)	1 (%8)	2 (%50)	5 (%13)
	2 (31)	23 (%38)	8 (%28)	0 (%0)	23 (%29)	8 (%61)	0 (%0)	15 (%37)
	3 (32)	19 (%31)	9 (%31)	4 (%67)	27 (%34)	3 (%23)	2 (%50)	19 (%47)
P Value		**p: 0.412**				**p: 0.348**		**p: 0.004**

We did not find any significant correlation between age and PR staining rate and intensity ((r:0.02, p=0.782), (r:0.02, p=0.811)). Likewise, there was also no significant correlation between gender and PR staining and intensity ((p=0.092), (p=0.533)). The evaluation of the WHO grade distribution did also not display any significant correlation with age and gender (p=0.491, p=0.672 respectively).

The WHO Grade distribution and PR positivity evaluation showed that the PR positivity was 87% and 95% in WHO Grade I and WHO Grade II respectively, while it was 100% in WHO Grade III.

We assessed the relationship of WHO Grade and PR staining rate and intensity and found a weak correlation between the WHO Grade and PR staining rate (r:0.22, p=0.028). We observed that the PR staining rate increased slightly with the increase of WHO Grade. Likewise, there was a weak correlation between the WHO Grade and PR staining intensity (r:0.30, p=0.002). We determined a slight increase in the PR intensity with the WHO Grade increase (Table 1). We also found that there was a moderate correlation between the WHO Grade and PR staining and intensity in males; the PR staining rate and intensity increased with the grade (r:0.22, p=0.028 and r: 0.54, p<0.001 respectively). In women, there was no significant correlation between WHO Grade and PR staining rate and intensity.

We investigated the correlation between the Ki67 proliferation index and PR rate and intensity and found no correlation (r:0.01, p=0.344). Similarly, there was no significant correlation between the mitotic activity and PR rate (r:0.10, p=0.327) (Table 2).

We investigated the relationship between brain invasion and PR rate and intensity. PR staining rate and intensity were slightly increased in cases with brain invasion with a weak correlation (r:0.21, p=0.037 and r:0.28, p=0.004) (Table 2).

DISCUSSION

In our study, some of our findings conflicts the results reported in the literature. We found PR positivity in the majority of the cases. There was no relationship between age, gender, and PR staining-intensity. The PR staining rate and intensity showed increase with WHO Grade. We also found a correlation between brain invasion and PR staining rate and staining intensity. There was no relationship between the Ki67 proliferation and mitotic activity and PR staining rate, staining intensity.

Meningiomas, which are the most common primary intracranial tumors, have usually a benign character. However, they have high mortality (61%) in inoperable patients (9). It was reported that meningiomas are twice more common in females compared to males and it was related to the hormone receptor expression (1). In this context, our study was consistent with the literature and our female: male ratio was of 1.8/1. Studies focused on the hormone receptor positivity reported different results. While 68% of meningiomas are PR positive, oestrogen and androgen receptor expressions are relatively uncommon (1). Khalid et al. detected PR positivity in all patients, other studies reported equal to or higher rates than 64% (10-13). Besides, these high rates, Kim et al. and Schrell et al. reported PR positivity rates of 31.9% and only 10% respectively (14). In our study, the PR positivity rate was quite high (90.6%), which was consistent with many studies in the literature.

The relationship between age and gender and the PR positivity was subject to many studies and it was reported that there was no correlation between the age and PR positivity (7, 10). Our study was consistent with other studies for this parameter. Studies focused on the relationship between gender and PR positivity reported conflicting results. Along with the studies reporting significantly higher PR expression rate in females compared to males (2, 11), there were some studies reporting higher PR positivity rates in males compared to females (15). Furthermore, some other studies reported that there was no significant difference between the genders (9). In our study, we did not detect any correlation between gender and PR positivity. There was also no significant correlation between the PR staining rate and intensity and the age and gender (p=0.092 and p=0.533 respectively).

Although there is a consensus on the presence of PR expression in meningiomas and the role of PR in the tumorigenesis, the results of the studies related to the WHO Grade and prognostic parameters and PR expression are inconsistent and there is no clear consensus. Several studies are present in the literature with conflicting results. Some of those report a positive correlation between PR expressions and grades however, there are also some studies reported negative correlation or no correlation at all.

Mukherjee et al. reported 70% and 20% PR positivity in patients with Grade I and II meningiomas respectively. Only one patient with WHO Grade I was included in this study and this patient was PR negative (2). In a study conducted by Carroll et al., an inverse correlation between the PR expression and histological grade was found (13). Nagashima et al. reported a loss in the PR expression in malignant variants (16).

In separate studies conducted by Markwalder et al. and Perrot-Applanat et al., no significant correlation between the WHO Grade and PR expression was found (11,17) . Hsu et al. observed a decrease in the PR expression in patients with Grade III meningioma and reported similar staining patterns in patients with Grade I and Grade II meningioma (12). Likewise, Ikeri et al. divided the PR expression into two groups as negative and positive and reported that there was no significant difference between the Grade I and Grade II meningiomas for the PR expression (9).

Unlike other studies, Fakhrjou et al. reported in their recently published study that the PR expression was a marker for the poor prognosis. In the same study, the

separate assessment of the histological grades showed that Grade I and Grade III tumors exhibited similar high PR expression and strong staining pattern. However, it was reported that the PR staining rate at Grade II level is higher in the Grade II meningiomas compared to Grade I and Grade III meningiomas. Taking into consideration the studies suggesting that PR expression is not related to prognosis and that PR expression rates and intensity in their study did not follow a rational sequence, they suggested that PR expression could not have prognostic value (8).

In our study, while 13% of Grade I and 5% of the Grade II tumors were PR negative, we did not observe PR negativity in Grade III tumors. In addition, we observed grade 3 staining in 36% of Grade I, in 50% of Grade II and 40% of the Grade III meningiomas. We found a weak correlation between the grade and PR rate and we observed a slight increase in the PR staining rate with the increase of the tumor grade. This rate was particularly more significant in males compared to females. The data obtained in our study showed that the increased PR staining rate and intensity have a weak correlation with a high grade in meningiomas, which was more significant in the male gender. Besides, almost all studies in the literature were conducted on patient populations, which were not homogeneous in terms of WHO Grade. Furthermore, PR expression was evaluated as negative or positive, a quantitative value was not determined according to the expression rate or intensity in PR-positive cases. In our study, we tried to determine a quantitative value. If the statistical analyses in the studies can be done with quantitative values according to the PR expression rate and intensity, we believe that more reliable results can be obtained. The study design that included the WHO classification according to 2016 WHO Central Nervous System Tumors Classification was another distinguishing feature of our study. According to the 2016 WHO classification, WHO Grade II meningioma can be diagnosed only with the presence of brain invasion (atypical meningioma) (4). Almost all studies focused on the relationship of PR and histological grade had been conducted before 2016 and, patients with brain invasion, who had been previously diagnosed with WHO Grade I meningioma, are now classified as WHO Grade II. Therefore, we believe that there is a need for studies, which have to be conducted with larger study populations with established diagnosis according to the new classification system and have cases evenly distributed for each WHO grade.

In studies focused on the PR expression in meningioma cases with brain invasion, no correlation had been found between the brain invasion and PR expression (18,19). In our study, we found a weak correlation between the brain invasion, which is an important prognostic parameter and an independent criterion for the determination of the WHO Grade, and the PR staining rate and intensity. In addition, studies reported that brain invasion was more common in males compared to females (20). In our study, no significant relationship was found between brain invasion and gender (p: 0.242).

Wolfberger et al. reported that there was no significant correlation, although the Ki67 proliferation index was higher in PR-negative meningiomas (21). Again, other studies stated that there was no relationship between the Ki67 proliferation index and mitotic activity and PR rate (11,19,22) . In our study, we did not find any correlation between the Ki67 proliferation index, mitotic activity, and PR staining rate and intensity, which was consistent with the literature. Although we ended up with interesting findings, the small study population was one of the limitations of our study.

CONCLUSION

In our study, we observed a weak positive correlation between the PR staining rate and WHO Grade and brain invasion in conclusion. On the other hand, there was no relationship between other important prognostic parameters like the Ki67 proliferation index, mitotic activity. From this aspect, our study did not have the sufficient statistical data that support the hypothesis in which PR is an indicator of poor prognosis. However, our findings pointed at the necessity of the revision of the relationship between PR and WHO Grade, which is a prognostic parameter. Although our findings results might be a guide way for the diagnosis, prognosis, and treatment of meningiomas, there is still a need for studies with larger sample sizes, which will be based on quantitative values and updated classification.

Competing interests: The authors declare that they have no competing interest.
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Ethical approval: The study was approved by the Local Ethics Committee (B.30.2.ATA.0.1.00/543).

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