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Original Research Article

Expression of Progesterone Receptor in Meningioma: A Tertiary Care Experience

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Abstract

Context: Meningiomas constitute about 13-26% of primary intracranial tumours. Although most of the meningiomas are benign grade I tumours, they show a recurrence rate of about 30%. Detection of morphologically benign and biologically aggressive meningiomas cannot be made by routine histology alone. Thus in the present study progesterone receptor was used as an adjuvant approach in the identification of these biologically aggressive meningiomas. *Aim:* The aim of the study was to assess the histological grade and subtype of meningiomas and to correlate their expression with progesterone receptor in non-recurrent and recurrent tumors. *Methods and Material:* This was a prospective study conducted over a period of one year from July 2013 - June 2014 in the Department of Pathology, Coimbatore Medical College and Hospital, Coimbatore. Thirty cases of meningioma were assessed histologically and immunohistochemically and correlated with various clinicopathological parameters. *Statistical analysis used:* Correlation between the histopathological results and immunohistochemistry results were calculated by using chi-square tests and test of sample proportion. *Results:* Thirty cases of meningioma were included in the study all of which were grade I tumours. Mean age of all cases was 45 years. Females outnumbered males with Female: Male ratio of 2.7:1. Progesterone receptor positivity was seen in about 19 out of 30 cases (63.3%). Progesterone receptor immunoreactivity was higher in females (68%). Age, location of tumour and subtypes had no correlation with progesterone receptor status. Recurrence was noted in 23% of cases (7 out of 30 cases). The recurrence rate was found to be higher in males (25%). Progesterone expression was higher in nonrecurrent tumours (78%).

Conclusions: The expression of progesterone receptor was associated with lesser recurrence and better prognosis. Progesterone receptor can be used along with other histological parameters for prognostication of meningiomas. Thus, in the grading of meningiomas, histopathological examination alone is not sufficient, ancillary tests with Progesterone receptor should be included for prognostication of meningiomas.

Keywords: Meningioma; Progesterone receptor; prognosis.

Introduction

Meningioma is the commonest primary intracranial neoplasm constituting about 25-30% incidence worldwide and the frequency of its occurrence has increased in recent days especially in female population. However, the exact etiology is still vague and multiple etiological factors have been postulated. Recent studies have shown that meningiomas express sex hormone receptors especially the estrogen and progesterone receptors which is a promising lead into the etiology, prevention and management of intracranial meningiomas.

Meningioma is thought to arise from meningeal cap cells which are not normally a target tissue for estrogen, progesterone action. However, numerous studies have showed the role of progesterone in growth and development of meningiomas.

Higher incidence of meningiomas is seen in the women of reproductive age group, when there is maximal gonadal activity. Also there is clinical and radiological evidence of rapid tumor progression during pregnancy and luteal phase of menstrual cycle.

Numerous studies have shown progesterone expression and to a lesser extent estrogen receptor expression in most of the meningioma specimens. Predicting the behavior of meningiomas with routine histopathological examination alone is not sufficient. Various literatures have shown that the expression of progesterone receptor is associated with lesser recurrence and better prognosis of patients. Thus our study was aimed at assessing the expression of hormonal receptors mainly the progesterone receptor in the meningioma specimens and to correlate them histomorphologically.

The following were the objectives of this study:

1. To assess the histological grade and subtype of meningiomas and
2. To correlate their expression with Progesterone receptor in non-recurrent and recurrent tumors.

Materials and Methods

This study was a prospective study conducted over a period of a year from July 2013 to June 2014 at Coimbatore Medical College and Hospital, Coimbatore, India. The ethical clearance was obtained from the Institutional Ethics Committee.

Thirty cases of meningioma were analyzed. All specimens of meningiomas received in the department were included in the study. Patients who received prior radiotherapy and chemotherapy were excluded from the study.

Processing and staining

The specimens were fixed in 10% formalin and subjected to routine tissue processing and 4-6 µm were cut on a glass slide for routine Hematoxylin and Eosin staining. The diagnosis of meningiomas were made by analyzing characteristic histopathologic features.

Sections were then deparaffinized in xylene and dehydrated in graded alcohol and water. Antigen retrieval was done. Sections were treated with peroxide block followed by application of primary antibody (supplied by biogenex) and super-enhancer. Then DAB chromogen was applied with substrate buffer and counterstaining was done with Haematoxylin.

Evaluation

The entire section in a slide is examined under high power objective for the presence of positive immunoreactivity. Tumor cells are read positive if there is golden brown nuclear staining of the neoplastic cells. Semiquantitative scoring was carried out.

Grading of intensity staining:

0-absent, 1-weak, 2-moderate, 3-strong

Percentage of positive tumor cells:

0-absence of positive tumor nuclei, 1- 10% of cells are positive, 2- 10-50% of cells are positive, 3-

51-80% of positive tumor cell nuclei, 4- >80% are positive tumor cell nuclei.

Progesterone receptor was read as positive if >10% of cells showed strong immunostaining or >50% of cells show moderate staining.

Statistical analysis

Correlation between the histopathological results and immunohistochemistry results were calculated by using chi-square tests and test of sample proportion.

Results

Age distribution

In the present study, 53% of cases were above forty years of age and the remaining 46% of the cases were below forty years of age. The mean age at presentation was 45 years in our study.

Sex distribution

The female sex had a greater predilection for meningiomas than men in our study. The female and men constituted around 73% and 27% of the total cases respectively. The female: male ratio in our study was found to be 2.7:1.

Location of the tumor

In our study we found that 63% of the meningiomas were supratentorial in location, followed by spinal meningiomas and infratentorial meningiomas constituting 23% and 13% respectively.

Subtype of the tumor

Most of the meningiomas in our study were grade I tumors. The most common subtype was transitional (Fig. 7) constituting 50% of the cases followed by meningothelial (Fig. 6) and fibrous types (Fig. 5) constituting 23% and 17% respectively. The psammomatous (Fig. 3) and angiomatous (Fig. 4) constituted 7% and 3% respectively.

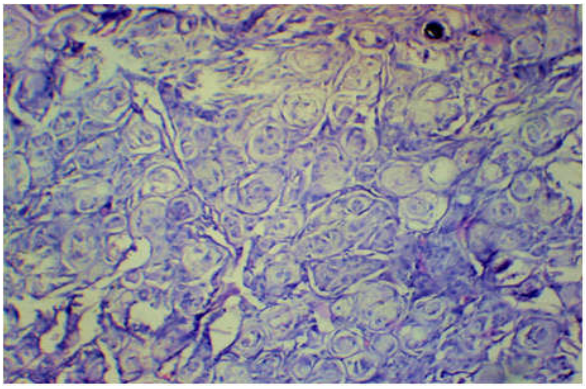

Fig. 1: Low power view of Meningioma showing whorls and psammoma Body -H&E(10x)

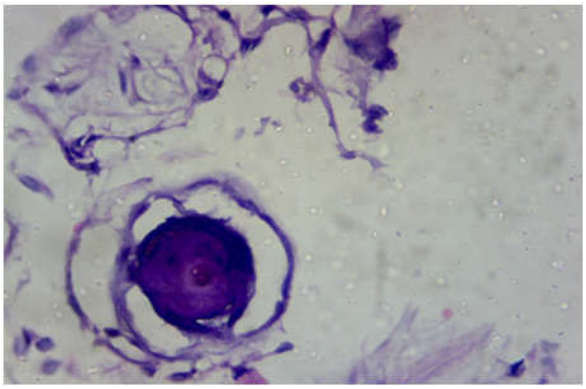

Fig. 3: High power view showing psammoma body -H&E (40x)

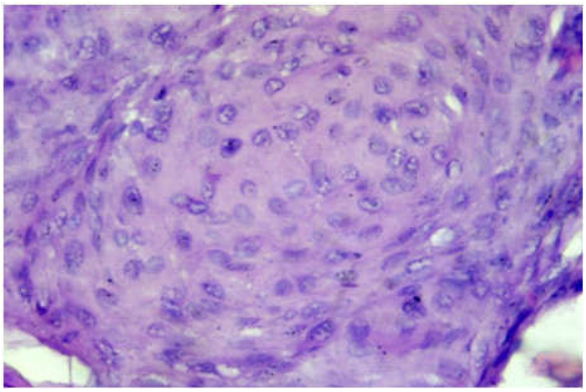

Fig. 2: High power view showing meningeal whorls- H&E (40x)

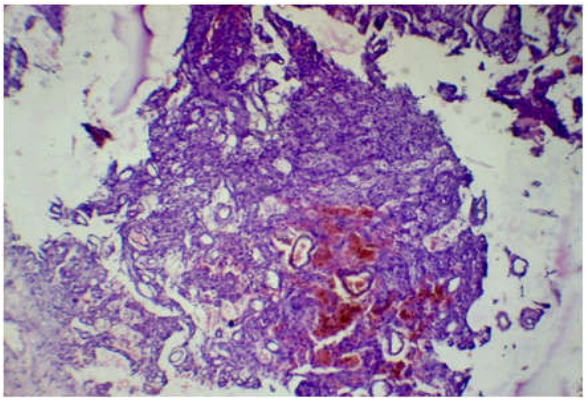

Fig. 4: Low power view of angiomatous type of meningioma-H&E (10x)

Expression of Progesterone receptor

In the study we found that 63% of the meningiomas expressed progesterone receptor (Figures 8,9,10) and 37% were negative for its expression.

Correlating age with expression of progesterone receptor

In our study we found that patients who were below forty years of age expressed progesterone receptor in 79% of the cases (11 out of 14 cases) and 21% (3 out of 14 cases) were negative for the expression of progesterone receptor.

The patients who were above forty years of age expressed progesterone receptor in 50% of cases and the remaining 50% did not express progesterone receptor (8 were positive out of 16 and 8 were negative). The results were analyzed using chi-square analysis and was found to be statistically insignificant (p value + 0.074).

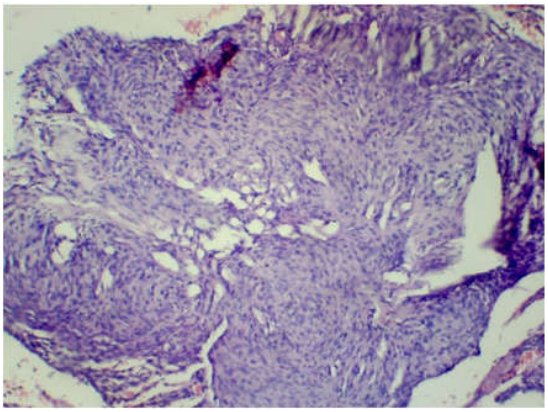

Fig. 5: Low power view of fibrous type of meningioma -H&E (10x)

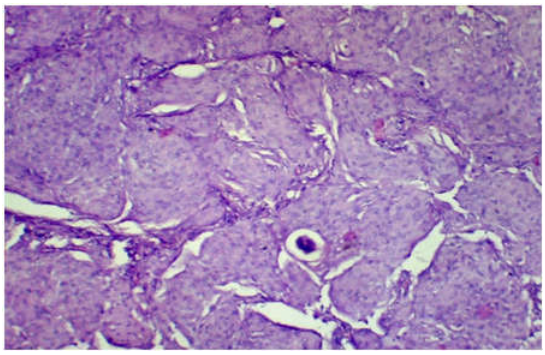

Fig. 6: Low power view of meningothelial type of meningioma- H&E (10x)

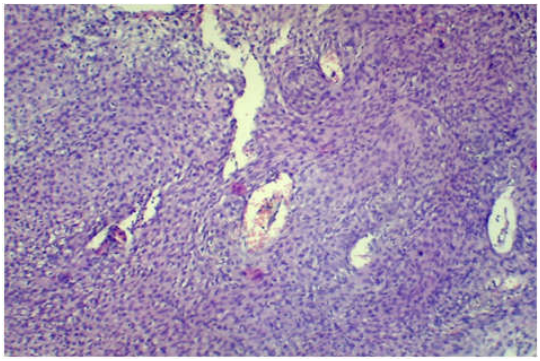

Fig. 7: Low power view of transitional type of meningioma H&E (10x)

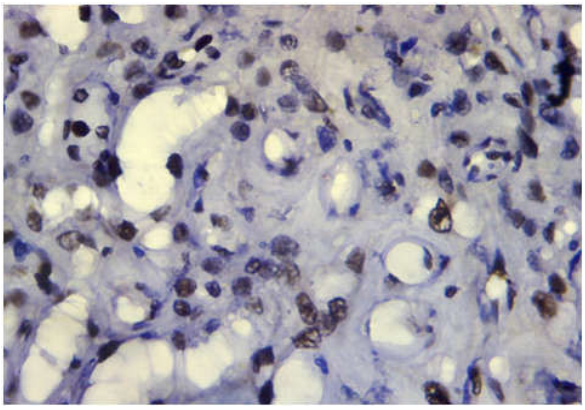

Fig. 8: Progesterone receptor positivity in angiomatous meningioma

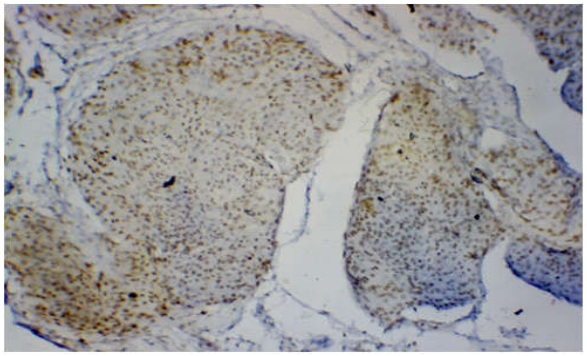

Fig. 9: Progesterone receptor positivity in meningothelial meningioma

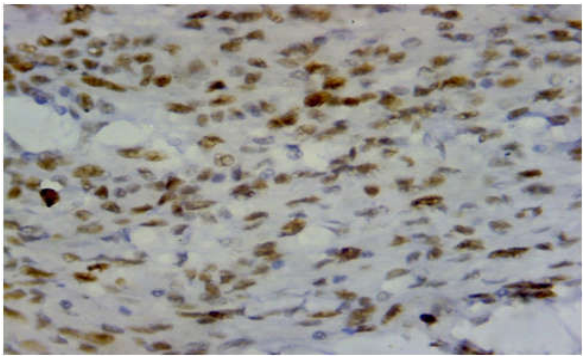

Fig. 10: Progesterone receptor positivity in transitional meningioma

Correlating sex with expression of progesterone receptor

The female patients in our study expressed progesterone receptor in 68% of the cases (15 out of 22) and 32% of the cases did not express progesterone receptor (7 out of 22). The chi-square analysis showed p value of 0.03 which was statistically significant.

Correlating subtype with expression of progesterone receptor expression

The percentage of expression of progesterone receptors in various subtypes of meningiomas were as follows: 100% in angiomatous, 73% in transitional, 60% in fibrous, 50% in psammomatous and 43% in menigothelial. The results were analyzed by using chi-square analysis and was found to be statistically insignificant with p value of 15.7.

Correlating the location of meningiomas with progesterone expression

In our study we found that 68% (13 out 19 cases) of cases of supratentorial meningiomas expressed progesterone receptors. The spinal meningiomas and infratentorial miningiomas expressed progesterone receptor in 57% (4 out of 7) and 50% (2 out of 4) respectively. The chi-square analysis showed p value of 0.67 which was statistically insignificant.

Incidence of recurrence

The recurrence was seen in about 23% (7 out of 30) of the grade I meningiomas and 77% (23 out of 30) of the grade I meningiomas were non-recurrent.

Correlating age with recurrence

In patients who were less than forty years of age only 2% (2 out of 14) of the cases showed recurrence and in patients above forty years of age 31% (5 out of 16) of the cases showed recurrence. The chi-square analysis showed p value of 1.02 which was statistically insignificant.

Correlating sex with recurrence

The study showed that recurrence in males constituted 25% (2 out of 8) and that in females constituted only 23% (5 out of 22). The chi-square analysis showed p value of 0.01 which was statistically significant.

Correlating recurrence with expression of progesterone receptor

In our study we found that the non- recurrent tumors expressed progesterone receptor in 78% (18 out of 23) of the cases and the recurrent tumors expressed in only about 14% (1 out of 7) of the cases. The chi-square analysis showed p value of 0.03 which was statistically significant.

Discussion

Meningiomas constitute the single largest group of tumor arising from the meningothelial cells [1]. It can range from benign meningioma (WHO grade I) to atypical and anaplastic meningioma (WHO grade II and grade III) respectively [2]. Meningioma constitute about 13-26% of primary intracranial tumors. The annual incidence rate of meningioma is about 6 per 100000 populations. The benign meningiomas constitute the majority of cases followed by atypical and anaplastic meningioma. Yet benign grade I meningiomas have an increased tendency to recur [3]. Even though tumor grade and subtype are strong prognostic factors, benign biologically aggressive meningiomas cannot be identified by routine histology alone. Hence the need for identification of newer prognostic indicators arises, to predict the clinical behavior. Various literature have shown that detection of progesterone receptor might predict the clinical behavior of meningioma and patient survival [4-5].

In the present study the expression of progesterone receptor were studied in the meningioma specimens and their possible correlation were analysed demographically, histomorphologically and by immunohistochemistry.

Thirty cases of meningioma were included in the study. The age of patients diagnosed as meninigioma ranged from 27 – 75 years. The mean age was 45 years (Table 1). This is in accordance with the results by El-Badawy et al. in which mean age was 46.7 years [6]. A study by Shalinee Rao et al showed mean age was 52.9 years [7].

Out of thirty cases of meningioma studied, females were twenty two in number and males were eight in number. Females constituted around 73.3% and males were 27%. The female: male ratio was 2.7:1 (Table 2). This is similar to the study by Ashraf Fakhrjou et al. [8], in which out of 50 cases, females were 76.5% (n=26), males were 23.5%. Shalinee Rao et al similarly showed an increased female: male ratio with 1.4:1 [7].

Among thirty cases studied, nineteen cases

were supratentorial in location, seven cases were spinal (23%), and only 4 cases were infratentorial in location (Table 3).

The various subtypes of meningioma in the study were transitional type, meningothelial type, fibrous type, angiomatous and psammomatous subtypes. Of these transitional meningioma was found to be the most common subtype, constituting about 50%, followed by meningothelial subtype which constituted around 23%. The other subtypes were fibrous, angiomatous, and psammomatous which constituted around 17%, 13% and 7% respectively (Table 4). A study by Shayanfar et al., showed meningothelial subtype to be the most common of all constituting around 40% followed by transitional and fibrous constituting about 36% and 24% respectively [9]. A study by Al-Nuaimy et al. also showed a similar result [10].

Among the thirty cases studied nineteen cases were progesterone receptor positive and eleven cases were progesterone receptor negative which constituted 63% and 37% respectively (Table 5). Similarly the expression of progesterone receptor in various other studies are as follows. According to Al-Nuaimy et al., progesterone receptor positivity was present in 72% of cases with 28% negative [10]. In the study done by Taghipur et al., the progesterone receptor positivity was noted in 68.6% of cases [11]. Thus comparing all the above studies there is a consistent expression of progesterone receptor positivity of more than 50%, which correlated well with our study.

Progesterone receptor positivity was correlated with the age of the patients. Of the total thirty cases, patients with age less than forty years were fourteen in number constituted around 46.6% and patients with age equal to or more than forty years, were sixteen in number which constituted about 53.3% (Table 6). Out of the fourteen cases with age less than forty years, progesterone receptor positivity was observed in eleven cases constituting 78.5% and three cases constituting 21% were progesterone receptor negative. Out of sixteen cases with age more than forty years the progesterone receptor

Table 1: Age wise distribution of meningiomas in our study

Age	Cases (Total number is 30)
<40 years	14 (46.6%)
>40 years	16 (53.3%)

Table 2: Sex distribution of meningiomas in our study

Sex	Percentage of cases
Females	22 (73%)
Males	08 (27%)

Table 3: Location of meningiomas in our study

Location	Cases
Supratentorial	19 (64%)
Infratentorial	4 (13%)
Spinal	7 (23%)

Table 4: Incidence of various subtypes of meninigioma

Subtype	Percentage in the study
Meningothelial	23%
Transitional	50%
Fibrous	17%
Psammomatous	7%
Angiomatous	3%

Table 5: The expression of progesterone receptor by the meningiomas

Progesterone status	Percentage
Positive: 19	63.3%
Negative: 11	37%

expression was not significant. Thus progesterone receptor positivity was observed higher in patients less than forty years. These results were analysed by chi-square analysis and p value was 0.074 which was insignificant. However, a study by Al-Nuaimy et al., progesterone receptor was positive in age group of 41-50 years which is slightly higher in age compared to the present study [10]. Also Roser et al. showed mean age of progesterone receptor positivity to be 55.4 years for females and 51.5 years for males [12].

Progesterone receptor positivity was correlated with the sex of the patients. Among the thirty cases, twenty two were females and eight were males. Out of twenty two females, progesterone receptor positive immunoreactivity was observed in fifteen cases which constituted around 68% and the remaining seven cases were progesterone receptor negative which is 37%. Among the eight males studied, progesterone receptor positive and negative cases were 50% each (Table 7). In a similar study by Al-Nuaimy et al., progesterone receptor was expressed in 72% of females and 20% of males [10]. Another study by Taghipour et al., 80% of female cases showed progesterone receptor positivity similarly 67.5% of females cases showed progesterone receptor positivity [11].

The percentage of progesterone receptor positivity in various subtypes were as follows: (Table 8) Grade I meningioma subtypes observed in the present study were transitional, meningothelial, fibrous, angiomatous, psammomatous. Progesterone receptor status was analyzed with the various subtypes observed in our study. Progesterone receptor positivity was expressed by 100% of angiomatous subtype followed by transitional type which showed 73% progesterone receptor positivity. The other subtypes with progesterone receptor positivity in decreasing order is as follows-fibrous, psammomatous, meningothelial with 60%, 50%, 43% respectively. These results were analyzed using Chi-square test which showed p value of 15.7. Hence, progesterone receptor expression was insignificantly related to meningioma subtypes in our study. A study El-Badawy et al., in which meningothelial showed 100% progesterone receptor expression followed by transitional 50%, fibrous 33.3% [6]. Another study by Roser et al. [12] in showed angiomatous subtype with maximum progesterone receptor expression constituting about 66.6% followed by meningothelial 64.6%, psammomatous 60%, transitional 50% and fibrous 31.1%. These differing results could be explained by the various stem cell factors involved in the progesterone receptor expression in meningiomas.

Table 6: Correlation between age and the expression of progesterone receptor

Age	Positive expression of progesterone receptor	Negative expression of progesterone receptor
<40 YRS	11 (79%)	3 (21%)
>40YRS	8 (50%)	8 (50%)

Table 7: Correlation between the sex and the expression of progesterone receptor

Sex	Positive expression of progesterone receptor	Negative expression of progesterone receptor
Male	4 (50%)	4 (50%)
Female	15 (68%)	7 (32%)

Table 8: Expression of progesterone receptor in various subtypes of meningiomas

Subtypes	Positive expression of progesterone receptor	Negative expression of progesterone receptor
Meningothelial	43%	57%
Transitional	73%	27%
Fibrous	60%	40%
Psammatous	50%	50%
Angiomatous	100%	0%

Table 9: Correlation of the location of the tumour with the expression of progesterone receptor

Location	Positive expression of progesterone receptor	Negative expression of progesterone receptor
Supratentorial	13 (68%)	06 (32%)
Infratentorial	02 (50%)	02 (50%)
Spinal	04 (57%)	03 (43%)

Correlating the location of the tumor and progesterone receptor positivity (Table 9). In the present study, nineteen cases were supratentorial in location, seven cases were spinal, four were infratentorial in location. Of the total nineteen supratentorial cases, Progesterone receptor immunoreactivity was observed in thirteen cases which constituted about 68.42%. Of the seven spinal cases four were progesterone receptor positive which were around 57%. Infratentorial tumors showed equal progesterone receptor positive and progesterone receptor negative cases with 50% in each group. Thus progesterone receptor positivity was higher in supratentorial tumors than in spinal and infratentorial tumors. However Chi-square analysis showed a statistically insignificant relation between progesterone receptor expression and location of tumor ($p>0.05$). These results were similar to other study by Milenkovie et al in which no statistically significant correlation was obtained between progesterone receptor expression and location of the tumour [13]. From the thirty meningioma cases included in the study, incidence of recurrence was analyzed. The criteria for recurrence was: any known case of meningioma, previously diagnosed and proven as meningioma by histopathology, now again presenting with clinical, and radiological signs of meningioma and proved as meningioma by histopathology. Of the thirty cases, recurrence was seen in seven cases constituting 23% and non recurrent cases were twenty three in number constituting 77% (Table 10).

These results were similar to a study by El-Badawy et al., out of 30 meningioma cases, non recurrent and recurrent cases were equal constituting 50% each [6]. Similarly a study by Al-Nuaimy et al. [10], Total of 50 cases were studied in which non-recurrent cases were around 86% and recurrent cases constituted around 14%. In the present study, age distribution of recurrent tumors were analyzed. Cases less than forty years who presented with recurrence were around 14.2% and patients who were more than forty years constituted 31.2% (Table 11).

Similar results were seen in studies by El-Badawy et al., Al-Nuiamy et al., no correlation was observed between recurrence and age of the patients [6,10]. In the present study, sex wise distribution of recurrent tumors were analyzed two out of eight males showed recurrence which constituted 25%, whereas only five out of twenty two females constituting 23% showed recurrence (Table 12). These results were analyzed using chi-square analysis which is statistically significant with p value of 0.01. This is similar to study by El-Badawy et al. [6] which showed recurrence to be more common in males than females. Similar results were seen in a study by Al-Nuaimy et al. [10] in which recurrence was higher in males. Progesterone receptor positivity in non recurrent and recurrent tumors (Table 13). In the current study, progesterone receptor positive immunoreactivity was observed in 78% of non recurrent cases and 14% cases of recurrent cases. The results were analyzed using chi-square analysis which was statistically significant ($p=0.03$). Our results were similar to results obtained in study by Al-Nuaimy et al. [10] in which progesterone receptor positivity was observed as 72% and 42% in non-recurrent and recurrent tumors respectively. Also a study by Roser et al. showed a higher progesterone receptor positivity in primary or non recurrent tumors 53.5% than in recurrent tumors [12].

Table 10: Incidence of recurrence of meningioma

Cases	Number
Non recurrent (Primary)	23
Recurrent	7
Total	30

Table 11: Correlating the age with the recurrence of the tumour

Age	Non recurrent	Recurrent
<40 years	12 (86%)	02 (14%)
>40 years	11 (69%)	05 (31%)

Table 12: Correlating the sex with the tumour recurrence

Sex	Non-recurrent	Recurrent
Male	06 (75%)	02 (25%)
Female	17 (77%)	05 (23%)

Table 13: Correlating the tumour recurrence with the expression of progesterone receptor

Cases	Positive expression of progesterone receptor	Negative expression of progesterone receptor
Non recurrent	18 (78%)	05 (22%)
Recurrent	01 (14%)	06 (86%)

Conclusion

Meningiomas are categorized into three grades according to WHO classification. In general WHO grade I tumour behave in a benign fashion. However a small subset of tumours appear morphologically benign and biologically aggressive. Detection of these subset of meningiomas is not in routine practice. Thus the study of Progesterone receptor, was used as an adjuvant approach in the identification of these histologically "on the fence" tumours. Thirty cases of meningioma were included in the study, all of which were grade I tumours. Progesterone receptor positivity is seen in about 63.3% of cases. Progesterone receptor expression was higher in females (68%) in comparing with the males. Age, location of tumour and meningioma subtypes had no correlation with Progesterone receptor. The recurrence rate was found to be higher in males (25%). Progesterone expression was higher in non recurrent tumours (78%). In recurrent tumours, Progesterone receptor expression was decreased (14%). Age, Location of tumour and the meningioma subtypes has no role in predicting the recurrence. Although meningiomas express progesterone receptor, it is independent of Estrogen receptor, unlike the other hormone dependant tumours like breast and uterus. Expression of Progesterone receptor is associated with lesser recurrence and better prognosis. These observations re emphasizes the need to identify morphologically benign, biologically aggressive meningiomas which can be accomplished with the help of immunohistochemistry using Progesterone receptor. Progeterone receptor can be used along with other histological parameters for prognostication of meningiomas In the grading of meningiomas, histopathological examination alone is not sufficient, ancillary tests with Progesterone receptor should be included for prognostication of meningiomas.

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