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Status of Ki-67, Estrogen and Progesterone Receptors in Various Subtypes of Intracranial Meningiomas

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Abstract: Meningiomas are the most prevalent intracranial tumors in human being. Although, majority of these cases are of benign nature, malignant behavior might be seen in a number of patients. This study aimed to investigate the status of estrogen receptor, progesterone receptor and Ki-67 labeling index in different grades of surgical intracranial meningiomas. In this prospective study, 50 patients with intracranial meningiomas were operated at the department of neurosurgery, Tabriz Teaching Imam Reza Hospital; from February 2010 through January 2012. Tumor grade was determined histopathologically according to the World Health Organization (WHO) subtyping system. Status of estrogen and progesterone receptor, as well as the Ki-67 labeling index was determined by immunohistochemical approach and graded as 0 (absent), 1 (weak), 2 (moderate) and 3 (strong). The group of patients comprised 15 males (30%) and 35 females (70%) with a mean age of 71.76±10.20 (range: 49-87) years. WHO grades I, II and III tumors were reported in 68, 22 and 10% of the cases, respectively. Estrogen receptor, progesterone receptor and Ki-67 labeling index were detected in 20% (all grade 1), 98% (grade 1: 2%, grade 2: 22%, grade 3: 74%) and 38% (grade 1: 6%, grade 2: 22% and grade 3: 10%) of the cases, respectively. The rate of grade 1 estrogen receptor was significantly higher in WHO grade I tumors (29%) than in WHO grades II and III (zero for both, $p = 0.02$). Grade 2 progesterone receptor was significantly higher in WHO grade II tumors (72.7%) vs. WHO grades I (8.8%) or III (0%). On the other hand, the rate of grade 3 progesterone receptor was significantly higher in WHO grades I (85.3%) and III (100%) tumors than in WHO grade II (27.3%) ($p = 0.01$). The rate of grade 3 Ki-67 labeling index was significantly higher in WHO grade III tumors (100%) than in WHO grades I and II (zero for both, $p<0.001$). This study showed that firstly, estrogen receptor is seldom expressed in patients with meningioma; however, its presence means a good prognosis. Secondly, Ki-67 labeling index is a marker of poor prognosis in these patients. Thirdly, although, progesterone receptors are frequently expressed in meningioma, their prognostic role varies greatly and needs to be determined in further studies.

Key words: Meningioma, estrogen receptor, progesterone receptor, Ki-67, tumor grade

INTRODUCTION

Meningiomas constitute the most frequent intracranial Space Occupying Lesions (SOLs) with primary origin in human being (Chamberlain and Barnholtz-Sloan, 2011; Gelabert-Gonzalez and Serramito-Garcia, 2011); which has been reported even in some animals (Nourani and Ziaee, 2007).

These tumors originate usually from the dura mater and are found in many cases near the venous sinuses and adjacent to the dural inward folds. Based on the subtyping of the World Health Organization (WHO), meningiomas could be subcategorized as grade I, II and III. Although, majority of tumors are benign and of WHO grade I; WHO grades II (atypical) and III (anaplastic) lesions are not infrequent and show a higher tendency to metastasize or recur after treatment in comparison with those of grade I (Alahmadi and Croul, 2011; Herrmann *et al*., 2011).

Ionizing radiation is the only known risk factor for meningioma by now. However, it is claimed that there might be other inherent or environmental factors which could contribute, at least, to the prognosis of these patients. Among these possible factors are sex hormones (Cowppli-Bony *et al*., 2011) and various factors such as Ki-67 (Albayrak *et al*., 2011).

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The prognostic role of estrogen and progesterone receptors has been widely discussed in different conditions, particularly in breast cancer (Hashemi and Karami-Tehrani, 2006; Agyei-Frempong *et al*., 2008; Amin, 2009; Sahib *et al*., 2009).

This role is even more widespread for the status of Ki-67; such as in cases with hepatotoxicity (El-Kott and Owayss, 2008), some bacterial infections (Rezaii *et al*., 2008), cancers in animals (Bin-Meferij, 2009), tongue carcinoma (Sohrabi *et al*., 2009), benign and malignant skin lesions (Talghini *et al*., 2009) and lung malignancy (Priya *et al*., 2011).

The role of these factors in meningioma, however, is not fully understood and ongoing debate is still present in the literature (El-Shaer *et al*., 2007).

The present study aimed to investigate the immunohistochemical status of estrogen and progesterone receptors, as well as the Ki-67 expression altogether in patients with meningioma.

MATERIALS AND METHODS

Study design and patients: In this prospective cross-sectional study, 50 patients with intracranial nonmalignant meningiomas including 15 males (30%) and 35 females (70%) with a mean age of 71.76±10.20 years were recruited from Imam Reza Teaching Centre in Tabriz, from February 2010 through January 2012.

All the patients were operated on at of the ward neurosurgery in the same centre. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences. Informed written consents were obtained from the patients.

Procedures: Paraffin embedded specimens of meningioma were evaluated for histopathologic grading of the disease, as well as the status of estrogen and progesterone receptors and Ki-67 labeling index by a skilled pathologist. For tumor subtyping, hematoxylin and eosin (H and E) stained samples were examined according to the new WHO classification (Kleihues *et al*., 1993):

- **WHO Grade I: Benign:** Meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic
- **WHO Grade II: Atypical:** Chordoid, clear cell and atypical
- **WHO Grade III: Malignant:** Papillary, rhabdoid and anaplastic

Briefly, the excised tumor tissues were immediately fixed with appropriate fixative (4% Paraformaldehyde). Then the fixed tissues were cut into appropriate portions and placed in embedding cassettes. Dehydration was performed using serial ethanol solutions (70-100%) for paraffin embedding at 56-58°C. At the time of histopathological examination, 2 μm thick paraffin-embedded tumor sections were produced by a microtome and following steps were conducted thereafter, deparaffinization (exposure the specimen to 60°C for 1 h), rehydration (using distilled water, 100% alcohol, Xylene), inactivation of the endogenous peroxidase (by 3% H_2O_2 plus methanol), washing with water, transferring the specimens to the Phosphate Buffered Saline (PBS) with the pH of 7.2, incubation with monoclonal antibodies against estrogen receptor, progesterone receptor and Ki-67 (Dako, Glostrup, Denmark) according to the guidelines provided by the factory, separately in the room temperature for one h, washing with the PBS and adding 3,3-diamino Benzidine substrate.

An optical grid (Zeiss, Germany) was employed at high power (400X) for examination of immunoreactivity. Tumors with strong staining in at least 10% of nuclei or moderate staining in about 50% of nuclei were considered estrogen/progesterone receptor positive. Positive results for Ki-67 were reported when the cells presented nuclear brown-colored staining pattern. The status of estrogen receptor, progesterone receptor and Ki-67 was determined semiquantitatively (percent positive tumor cells) and graded as zero (absent, indicating the absence of positive nuclei), 1 (weak, the presence of a few positive tumor nuclei, 10% in the entire section), 2 (moderate, an estimated 10-50% positive nuclei) and 3 (strong, 50%<positive tumor nuclei) (Roser *et al*., 2004).

Negative controls were run at each staining session, as were positive control specimens using breast cancer tissue for estrogen and progesterone receptor and lymph node germinal center for Ki-67.

Data: Patients' demographics (age and gender), as well as the status of Ki-67 labeling index, estrogen receptor and progesterone receptor were determined and stratified by the grades of tumor.

Statistical analysis: The variables were shown as Mean±SD or number (%). The SPSS software for Windows (ver.15) was used for analysis. The One-way ANOVA test or the contingency tables (Chi-square or Fisher's exact tests) were employed for statistical comparisons. The $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 50 patients with surgical intracranial meningioma were studied. Based on the WHO grading system, there were 34 specimens with WHO Grade I tumor, 11 specimens with WHO Grade II tumor and 5 specimens with WHO Grade III tumors. Percentage of the patients as to the grade of tumor is shown in Fig. 1.

The age of patients ranged between 49 and 87 years. This range was between 50 and 85 years in the group with grade I tumor, between 49 and 84 years in the group with grade II tumor and between 51 and 87 years in the group with grade III tumor. In total and in each group, female patients predominated. The patients' age, as well as their gender is summarized in Table 1. The three groups were comparable in terms of age (p = 0.79) and gender (p = 0.19) (Table 1).

Estrogen receptor was absent (grade zero) in 40 cases (80%) and of grade 1 in the remaining 10 cases (20%).

Progesterone receptor was absent in 1 case (2%), of grade 1 in another case (2%), of grade 2 in 11 cases (22%) and of grade 3 in 37 patients (74%).

Ki-67 labeling index was absent in 31 cases (62%), of grade 1 in 3 cases (6%), of grade 2 in 11 cases (22%) and of grade 3 in 5 cases (10%).

Zero grade estrogen receptor was reported in 24 (70.6%), 11 (100%) and 5 (100%) cases in groups with WHO grades I, II and III tumors, respectively. The estrogen receptor of grade 1 was only present in 10 patients (29.4%) in the group with WHO grade I tumor (Table 2).

Accordingly, the percentage of cases with grade 1 estrogen receptor was significantly higher in the patients with WHO grade I tumor than in those with WHO grades II and III tumors (p = 0.02). In other words, expression of estrogen receptor means a milder meningioma and a good prognosis.

Grade zero, 1, 2 and 3 progesterone receptors were respectively detected in 1 (2.9%), 1 (2.9%), 3 (8.8%) and 29 (85.3%) cases with WHO grade I meningioma, 0 (0%), 0 (0%), 8 (72.7%) and 3 (27.3%) cases with WHO grade II meningioma and 0 (0%), 0 (0%), 0 (0%) and 5 (100%) cases with WHO grade III meningioma (Table 2).

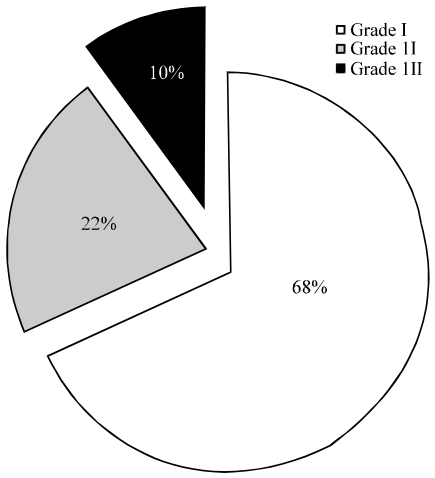

Fig. 1: Presence of intracranial meningioma in patients according to WHO grades

Table 1: Demographic analysis of studied patients with meningioma stratified by the WHO grade

	WHO grade				
Variables	I (n = 34)	II (n = 11)	III (n = 5)	Total (n = 50)	p-value*
Age (year)	72.41±10.14	70.00±10.35	71.20±12.01	71.76±10.20	0.79
Gender					
Male	8 (23.5)	5 (45.5)	2 (40)	15 (30)	0.19
Female	26 (76.5)	6 (54.5)	3 (60)	35 (70)	

*Between three groups of meningioma (I, II, III), Values are Means±SD or frequency, Values in parentheses are percentage p-value <0.05 is statistically significant

Table 2: Status of estrogen receptor, progesterone receptor and Ki-67 expression in the patients with meningioma stratified by the WHO grades

		WHO grade						
		I (n = 34)		II (n = 11)		III (n = 5)		
Marker	Marker grade (n)	No.	%	No.	%	No.	%	p-value
Estrogen receptor	0 (40)	24	70.6	11	100.0	5	100	0.02
	1 (10)	10	29.4	0	0.0	0	0	
Progesterone receptor	0 (1)	1	2.9	0	0.0	0	0	0.02
	1 (1)	1	2.9	0	0.0	0	0	
	2 (11)	3	8.8	8	27.7	0	0	
	3 (37)	29	85.3	3	27.3	5	100	
Ki-67	0 (31)	31	91.2	0	0.0	0	0	<0.001
	1 (3)	2	5.9	1	9.1	0	0	
	2 (11)	1	2.9	10	90.9	0	0	
	3 (5)	0	0	0	0.0	5	100	

p-value <0.05 is statistically significant

Accordingly, the rate of grades 2 progesterone receptor was significantly higher in the patients with WHO grade II tumor than in the patients with WHO grades I or III tumors ($p = 0.02$). These findings mean that the status of this biomarker is variable in the patients with meningioma and no prognostic significance could be readily drawn.

Grade zero, 1, 2 and 3 Ki-67 labeling index were, respectively reported in 31 (91.2%), 2 (5.9%), 1 (2.9%) and 0 (0%) cases with WHO grade I meningioma, 0 (0%), 1 (9.1%), 10 (90.9) and 0 (0%) cases with WHO grade II meningioma and 0 (0%), 0 (0%), 0 (0%) and 5 (100%) cases with WHO grade III meningioma (Table 2).

Based on these results, the rate of grades 2 and 3 Ki-67 labeling index was significantly higher in the patients with WHO grades II and III tumors (15 out of 16 cases, 93.8%) than in the patients with WHO grade I tumor (1 out of 34 cases, 2.9%) ($p<0.001$). This means that higher grades of Ki-67 labeling index predict more advanced meningioma or a poor prognosis.

DISCUSSION

In this study, status of three factors including estrogen and progesterone receptors, as well as Ki-67 labeling index was investigated immunohistochemically in surgical cases of meningioma and their possible association with grades of the disease was examined.

Based on the finding, estrogen and progesterone receptors were expressed positively in 20% (all of grade 1) and 98% (of grade 1 in 2%, grade 2 in 22% and grade 3 in 74%) of the cases, respectively. This rate was 38% (of grade 1 in 6%, grade 2 in 22% and grade 3 in 10%) for Ki-67 labeling index.

There was a significantly negative association between the expression rate of estrogen receptor and WHO grades of meningioma. Similar associations were significantly positive between the expression rate of progesterone receptor and Ki-67 index with the WHO grade of tumor. Briefly, both progesterone receptor and Ki-67 labeling index were predictors of poor prognosis; while estrogen receptor was an index of good prognosis. In a pioneer study, Bouillot *et al.* (1994) evaluated 52 patients with high histological grade of meningioma, in majority. They showed lack of estrogen receptors in all cases; however, progesterone receptors were present in 53% of the patients. They finally recommended future studies on well-defined meningioma subgroups.

Although, the rate of estrogen receptors was similarly low in our series, it should be reminded that the mentioned study recruited only cases with low-grade meningioma. As they have recommended, we enrolled well-defined meningioma subgroups (WHO classification). Although, they did not report the degrees of the expression of estrogen receptors, we showed that there was a reverse association between this factor and WHO grades of meningioma. This finding justifies the low rate of the expression of estrogen receptors in the mentioned report.

Gursan *et al.* (2002) investigated the presence of progesterone receptors in 110 patients with meningioma. They found that the progesterone receptors were negative in 28%, weakly positive in 20% and moderately to strongly positive in 52%. The rate of progesterone receptor positivity was higher in patients with benign disease, suggesting that progesterone may play a significant role in progression of meningiomas.

The rates of progesterone receptor positivity are similar in our study (negative/weekly positive in 4%, moderately positive in 22% and strongly positive in 74%) and the mentioned investigation. We also found a higher rate of strongly positive expression of this marker in WHO grade I, as well as in grade III tumors. This means that a role for progesterone may be acknowledged. However, this difference did not follow a logical sequence in our series; i.e. the rate of grades 2 progesterone receptor was significantly higher in the patients with WHO grade II tumor than in the patients with WHO grades I or III tumors. These findings mean that the status of this biomarker is variable in the patients with meningioma and no absolute prognostic significance could be drawn.

Takei *et al.* (2008) studied 57 patients with meningioma (grades I and II). The expression of estrogen and progesterone receptors was seen in 10.4 and 87.2% of cases, respectively. These rates are also in conformity with ours.

Pravdenkova *et al.* (2006) assessed the estrogen and progesterone status in 239 patients with meningioma. They found that estrogen receptors are predictive of aggressiveness of the disease; while progesterone receptors were related to benign condition in this group of patients.

Our findings are in contradiction with this report. In other words, there was a good prognostic role for the presence of estrogen receptors in our series with unspecified prognostic influence of progesterone receptors in this regard. It should be noted that in the mentioned study, in contrast with ours, the possible association of estrogen and progesterone receptors with the progression of the disease was not examined according to a well-accepted scale such as the WHO grading system in meningioma. Likewise Inhomogeneous grades of meningioma may justify this kind of heterogeneity.

For example, Shayanfar *et al.* (2010) studied 78 cases of meningioma in terms of Ki-67 and progesterone receptor status. The rate of Ki-67 positivity was 2.98, 9.30 and 34% in grade I-III tumors, respectively. These rates were 96.8, 20 and 0.5% for the status of progesterone receptor in grade I-III, respectively. Both parameters were significantly associated with the grade of tumor; i.e., they were considered good indices of poor prognosis.

As seen, they did report poor prognostic roles for both the Ki-67 index and progesterone receptor. The status of Ki-67 expression in our series was also similar to this report (of grade 1 in 6%, grade 2 in 22% and grade 3 in 10%). Furthermore, a poor prognosis in association with Ki-67 labeling index was also revealed in our study.

Despite available heterogeneity in terms of the prognostic role of estrogen and progesterone receptors in patients with meningioma, almost all previous reports have reached an agreement on the poor prognosis in association with Ki-67 labeling index. For example, Mukherjee *et al.* (2011) examined 60 patients with meningioma and assessed the expression of Ki-67 and progesterone receptor in various histological subtypes of the disease. Both the markers were significantly higher in the cases with higher grade tumors. In a meta-analysis, Abry *et al.* (2010) reported that the mean labeling indices of Ki-67 was 3, 8 and 17% for grade I-III meningiomas. They found a positive correlation between Ki-67 index and grade of the disease. This indicates a poorer prognosis in meningiomas with positive Ki-67 index. Maiuri *et al.* (2007) evaluated 50 patients with respected WHO I meningiomas. They found that Ki-67 and progesterone receptor negativity were predictive of recurrence in benign meningiomas. In another series by Mittal *et al.* (2012), 85 cases with meningioma were evaluated for presence of Ki-67 status. They did not find a positive correlation between this marker and poor prognosis of the disease. Babu *et al.* (2011) studied the rate of Ki-67 index positivity in 300 cases with meningioma. There was a significant positive correlation between this index and grade of tumors. In addition, the factor was significantly predictive of aggressiveness and recurrence in meningioma. In the present study the rate of grades 2 and 3 Ki-67 labeling index was significantly higher in the patients with WHO grades II and III tumors (93.8%) than in the patients with WHO grade I tumor (2.9%). This means that higher grades of Ki-67 labeling index predict more advanced meningioma or a poor prognosis. Thus, the results of the mentioned studies are in line with our finding regarding the prognostic role of Ki-67 index in patients with meningioma.

CONCLUSION

This study showed that firstly, estrogen receptor is seldom expressed in patients with meningioma; however, its presence means a good prognosis. Secondly, Ki-67 labeling index is a marker of poor prognosis in these patients. Thirdly, although, progesterone receptors are frequently expressed in meningioma, their prognostic role varies greatly and needs to be determined in further studies.

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