Original Research Paper

VOLUME - 4 | ISSUE - 1 | January - 2020 | ISSN (O) : 2663-2888 | ISSN (P) : 2663-287X

# KI-67 PROLIFERATION INDEX AND PROGESTERONE RECEPTOR STATUS IN DIFFERENT HISTOLOGICAL SUBTYPES AND GRADES OF MENINGIOMA. AT A TERTIARY CARE INSTITUTE IN NORTH WESTERN INDIA

| | |
|---|---|
| **Dr Akriti Khare** | Virologist, National Public Health Laboratory, |
| **Dr Jayanti Mehta** | MBBS, MD. Ex Professor, SMS Medical College Jaipur |
| **Dr Deepika Hemrajani** | MBBS, MD Associate Professor, SMS medical College, Jaipur |
| **Dr Ankur Shrivastava** | MBBS, MS. Neurosurgery Resident Goa medical college, Goa |

**ABSTRACT** **Context:** Meningiomas are the most common benign brain tumors. WHO grading system divides these tumours into three grades on the basis of histology. Some of the diagnostic histologic criterias for grading are vague and difficult to interpret. Few studies have reported expression of both Ki- 67 proliferative index and Progesterome receptor in different grades and histological subtypes of meningioma. **Aims:** To assess the expression of Ki-67 and progesterone receptor(PR)in different histological types and grades of meningiomas.**Settings and Design:** Hospital based retrospective stud **Methods and Material:** A total of 100 consecutive cases were collected over a period of one year. Haematoxylin and Eosin staining was done for histological typing and grading of tumors. Immonohistochemical staining was done for Ki-67 and PR and Ki-67 labelling index(LI) and PR score was calculated **Statistical analysis used:** Chi- Square test. **Results:** Mean Ki-67 LI showed an increase with increasing grades of meningioma. The difference in mean Ki-67 LI between Grade I and II was statistically significant. PR positivity was significantly higher in females versus males, in Grade I versus Grade II and in Grade I versus Grade III meningiomas. Moreover mean Ki-67 LI was significantly higher in PR negative versus PR positive meningiomas **Conclusions:** Evaluation of PR and Ki-67 LI along with conventional histologic evaluation can be useful to delineate aggressive cases from benign and in distinguishing between grades of meningioma especially in borderline cases when histology is difficult.

**KEYWORDS**

Meningioma, Ki-67, PR, Grading.

***Corresponding Author** Dr Akriti Khare

MBBS MD, Assistant Professor, PCMS and RC Bhopal , Ex Senior Resident, AIIMS Bhopal

**Introduction:**

Meningiomas are the most common benign tumors of brain, and account for 36% of primary central nervous system tumors.[1,2] WHO grading system divided these tumours into three grades on the basis of histology.[2,3] Some of the histologic criterias for diagnosing atypical and anaplastic meningiomas are vague and there is considerable interobserver variation in interpretation[4] Studies have reported that a good correlation exists in meningiomas between Ki-67(proliferative marker) expression calculated as Ki-67(MIB-1) Labelling Index( Ki-67 LI) and increasing grades of meningioma.[4-8]. However due to significant differences in technique and interpretation it is difficult to establish definitive cut off values.[2] Progesterone Receptor(PR) expression in meningiomas have also been studied.[9-13] This study was done to assess the expression of Ki-67 and PR in different histological grades and types of meningioma.

**Material and Methods:**

A total of 100 consecutive histopathologically confirmed cases of meningioma resected over a period of one year were included in this study. Clinical and demographic data about each patient was obtained through review of recquisition forms and included age, sex, clinical complaints, tumor location and radiological findings. Haematoxylin and eosin (H and E) staining was done for histological typing and grading of tumors. Tumors were graded according to the WHO grading system. Immunohistochemical staining was performed with monoclonal antibody for MIB-1 and PR. Three to four micrometer thin, formalin fixed, paraffin embedded tissue sections were taken on slides coated with poly-L-lysine. Sections were deparaffinised and dehydrated in xylene, absolute alcohol, 90% and 70%alcohol. Antigen retrieval was done in microwave using tri sodium buffer at pH six. Sections were treated with three percent hydrogen peroxidase to quench endogenous peroxidase activity. Sections were stained with antibodies and peroxidase antiperoxidase method was followed for secondary staining. DAB was used for colouring the antigen-antibody complex. Known positive controls ( breast carcinoma for PR and Tonsil for Ki-67) were run at each staining session.

Ki-67 Labelling Index(LI) was determined in each case by manual counting at 400X . A total of 1000 nuclei were counted in the most densely labelled microscopic fields and the Ki-67 Labelling Index was expressed as a percentage of positively stained tumor nuclei out of 1000 nuclei counted. PR expression was determined by a semiquantitative scoring scale with respect to staining intensity( graded as: 0, absent; 1, weak; 2, moderate; and 3, strong) and percentage of positive tumor cells (0, indicating the absence of positive nuclei, 1, the presence of a few positive tumor nuclei $< 10\%$ in the entire section; 2, an estimated 10-50% positive nuclei; 3, 51-80% positive tumor nuclei; and 4, $>$ 80% positive tumor nuclei). As verified with meningioma tissue, [9, 14] an immunoreactive score was calculated for each tumor by multiplying the staining intensity by the indicator of positive tumor cells, producing an IRS range from 0 to 12. Tumors with an IRS of two or more were considered receptor positive.

Staatistical analysis of data was performed using SPSS (version 12) software program. Quantitative data was assessed using mean, range and standard deviation (SD). Qualitative data was assessed by chi-square test. A P value $< 0.05$ was considered to be statistically significant. Our study was a retrospective study analysing previously reported cases. The institutional ethics committee granted approval of the study.

**Results:**

A total of 100 cases were studied. The mean age was 44 years with an age range of 11-75 years. Maximum patients were noted in the age group of 31-50 years. There were 56 female patients and 44 male patients with a M:F ratio of 1:1.27. Among middle aged persons(31-40years) there was marked female predominance with M:F ratio of 1:1.72. The most common location was frontal region( 18%) followed

VOLUME - 4 | ISSUE - 1 | January - 2020 | ISSN (O) : 2663-2888 | ISSN (P) : 2663-287X

by sphenoid wing (14%)and intraspinal (13%). According to histological type, 37 were meningothelial(37%), 34 transitional (34%), ten fibroblastic(10%), five angiomatous (5%), four psammomatous( 4%), three microcystic (3%), one secretory(1%)(Figure 1 and 2), there were three cases of atypical meningioma( Figure 3a) (3%), and one each of clear cell(Figure 3b,c), rhabdoid (Figure 4) and anaplastic meningioma( Figure 5) (1% each). According to WHO grading system, 94 cases were Grade I (94%), four cases were Grade II (4%) and two cases were Grade III meningiomas(2%). Among 94 cases of Grade I there were 53 female and 41 male patients with a M:F ratio of 1:1.29, while in Grade II and Grade III meningioma cases M:F ratio was 1: 1 with two male and two female patients of Grade II meningioma and one male and one female patient of Grade III meningioma.

We determined Ki-67 LIs of all the 100 cases. Mean Ki-67 LI in 44 male patients was 2.47%( SD = 6 .00) whereas in 56 female patients was 1.85% (SD = 3.07). No statistically significant difference of Ki-67 LI was observed in different histological subtypes of Grade 1 meningioma. ( Table 1). Mean Ki-67 LIs of 94 Grade I meningiomas ( mean LI: 1.30%, SD = 0.71)(Figure 6a) were significantly lower (P 0.0081 )than LIs of four Grade II meningiomas( mean LI: 6.75%, SD =1.75)(Figure 6b). Two cases of Grade III meningioma showed mean Ki-67 LI of 31.5%(SD = 5.66)( Figure 6c), but no statistically significant difference in LIs was observed between Grade III and Grade II( P 0.2074) and Grade I and grade III meningiomas( P 0.1746). We also analyzed Progesterone Receptor(PR) expression in all the 100 cases. PR positivity was found in 63 out of the100 cases of meningioma. Among 56 female patients, 40 showed positive PR staining (71.42%) whereas among 44 male patients 23 showed PR positivity (52.27%)and this gender related difference in PR expression was statistically significant (P 0.0489). In our study PR was positive in 63 out of 94 cases of Grade I meningiomas while none of the Grade II and Grade III tumors showed expression of PR(Figure 7A,B), there was statistically significant difference in PR expression between Grade I and Grade II (P 0.0145) and between Grade I and Grade III( P 0.0483). Among the histomorphologic subtypes of WHO Grade I meningiomas, PR expression was seen more frequently in meningothelial compared to other subtypes(Table 2). The Ki-67 LI of the PR negative tumors was significantly higher than PR positive tumors( P 0.0277). (Table 3)

**Discussion:**

High grade meningiomas have an aggressive behavior mainly determined by the histological grade.[2,3] Although the histologic criteria for diagnosis of high grade meningiomas are well defined in recent WHO classification, in some odd cases of meningioma establishing a diagnosis of high grade meningioma could be difficult.[2,7,15] Moreover there remains considerable variability in biological behaviour, growth potential and clinical outcome within each grade and thus the histologic parameters alone may be insufficient for prediction of aggressive behavior.[7,16-18]There are studies stating a good correlation between Ki-67(MIB-1) and grade in meningiomas.[4-7] Previous studies have stated the presence of significantly higher PR values in benign meningiomas compared with WHO grade II or III tumors, and that atypical and anaplastic meningiomas frequently lack PR.[9-14] There is some evidence that evaluation of PR status and Ki-67 LI together with histologic evaluation can provide a tool for estimating the biological behaviour of meningiomas.[4,12] The available data about relationship between expression of PR and Ki-67 LI in order to determine more precisely the potential of aggressiveness is limited. In the present study our aim was to investigate the Ki-67 LI ad PR expression in various grades and histologic subtypes of meningioma at a tertiary care institute catering to surrounding rural population in north western India.

In our study females comprised a greater percentage of cases compared to males (56% vs 44%) with an overall F:M ratio of 1.27:1 which was consistent with the earlier studies.[19,20] The F:M ratio in the 31-40 yrs age group was 1.72 and this finding was similar to Cordera et al21] (F:M ratio in middle aged patients 1.7:1 ). Our results showed the most common histological subtype as meningothelial(37%) followed by transitional(34%)and fibroblastic(10%) and this finding was similar to Gursan et al., (Meningothelial 50%> Transitional 29% >fibroblastic 16%).[12] However the frequency of meningothelial (37%vs 50%) and fibroblastic (10% vs 16%) was lesser and that of Transitional (34%vs 29%) greater compared to Gursan et al.[12] Anaplastic meningioma comprised 1% of all cases in our study and this was consistent with Willis et al.[22] and Perry et al.[23]

According to histological grade we found 94 cases of Grade I (94%), four cases of Grade II (4%) and two cases of Grade III(2%). So Grade III cases comprised of 2% cases in our study which was consistent with several other studies (Maier et al.-2.4%; Willis et al.-1.6%).[22,24] However Grade II cases comprised only 4 % cases in our study which was similar to Jaaskelainen et al.,(4.7%);[25] but deviated from Willis et al. (20.4 %).[22]

Amatya et al., [7] in their study stated that among benign meningiomas fibrous type had higher LIs than other histological subtypes. Our study deviated from this finding and showed no significant difference in Ki-67 proliferation index in histologic subtypes and this finding correlated well to Mukherjee et al., 2011.[26] In our study the mean Ki-67 labelling index showed an increase with increasing grade of tumor. Grade II cases showed a significantly higher Ki-67 LI compared to their benign counterparts (P 0.0081) and this finding is corroborative with the previous studie (Abramovich et al.,[5] Kayaselcuk et al.,[6] Gursan et al.[12]). Our study found a higher mean Ki-67 LI in Grade III versus Grade II but was unable to show a statistically significant difference among them. This finding was similar to Langford et al.[27] and Striepicke et al.[28] as our study too suffered from limitation of very low number of each of these tumor grades as the above studies.

Mean MIB 1 Labelling Index of two cases of grade III was much greater than of benign meningiomas, but this difference was statistically not significant (P>0.05). This deviated from earlier studies by Karamatopoulou et al.,[8] and Gursan et al.[12] and may be explained as to be the limitation of very small number of grade III tumors included in our study. Moreover, because staining and counting techniques for obtaining Ki-67 LIIvary significantly among different laboratories, it is difficult to decide upon a reliable cut off.[29] Although proliferation markers such as Ki-67 might provide valuable prognostic information,[6,7] they have not been included in the grading criteria, probably due to the high interinstitutional and interindividual variability with respect to their cut offs.[2,30]

We have found PR positivity in 63% of the cases which is close to study by Mukherjee et al.,[26] which showed PR positivity in 65% of the cases and Brandis et al.,[14] which showed PR expression in 61% cases. However there are different other studies (Gursan et al.)[12] which showed a little higher PR positivity(72%) as well as studies which showed lower PR positivity (F Roser et al. [9] 55.9%).

In our study the presence of PR immunostaining was more abundant in females (71% females vs 52% males) and this gender related difference was statistically significant . Earlier studies ( Gursan et al [12].; Mukherjee et al.,[26]) have also shown a significant gender difference in expression of PR, in that a higher percentage of women with meningioma have PR than do men. In our study we found PR expression more frequently in meningothelial compared to transitional or fibrous and this finding is consistent with that of earlier studies ( Roser et al., 2004[9] , Gursan et al.,[12] and Mukherjee et al.,[26])

Our Study included four cases of grade II(three atypical and one clear cell) and two cases of Grade III meningioma ( anaplastic and rhabdoid ) none of which expressed PR while 67%(63 out of 94) of Grade I tumors were positive for PR .In our study positive immunostaining rate for PR in Grade I meningiomas was significantly higher than in higher grade tumors which is similar to earlier studies.[9-12] We found PR positivity in 67% of Grade I meningiomas while Mukherjee et al.,[26] found 70% positivity in the same grade.

Earlier studies [9,12,13,26] have shown that PR negative tumors have higher MIB-1(Ki-67) Labelling Index compared to PR positive tumors. Our data confirmed that Ki-67 Labelling Index were significantly higher in the PR negative tumors compared to PR positive tumors.

To conclude the results of the present work indicate that in meningiomas Ki-67 Labelling Index shows an increase with increasing grade of tumor. Difference in MIB 1 LI between Grade I and Grade II

VOLUME - 4 | ISSUE - 1 | January - 2020 | ISSN (O) : 2663-2888 | ISSN (P) : 2663-287X

tumors was statistically significant indicating that MIB 1 can be helpful as an adjunct to grading in histologically borderline cases. Progesterone Receptor positivity is significantly associated with tumor grade, with higher grades showing loss of PR expression. PR positivity in females is greater compared to males similar to various national and international studies. Ki-67 LI in PR negative tumors is significantly greater compared to PR positive tumors. Thus a combination of PR and Ki-67 LI can be useful to delineate aggressive cases from benign and in distinguishing between grades of meningioma especially in borderline cases when histology is difficult.

**Tables**

**Table 1: MIB 1 Labelling Index in different histological subtypes of meningioma(n=100)**

| Histological Subtype | No. of cases | WHO Grade | Mean MIB1 LI |
|---|---|---|---|
| Meningothelial | 37 | I | 1.11 |
| Transitional | 34 | I | 1.63 |
| Fibroblastic | 10 | I | 1.27 |
| Psammomatous | 4 | I | 0.8 |
| Secretory | 1 | I | 1.8 |
| Microcystic | 3 | I | 1.63 |
| Angiomatous | 5 | I | 0.64 |
| Atypical | 3 | II | 6.6 |
| Clear cell | 1 | II | 7.2 |
| Rhabdoid | 1 | III | 23 |
| Anaplastic | 1 | III | 40 |

**Table 2:PR status in histological subtypes of Grade I meningiomas**

| Histological subtype | No of cases | No. of PR + cases | Percentage of PR + cases |
|---|---|---|---|
| Meningothelial | 37 | 28 | 75.67 |
| Transitional | 34 | 22 | 64.70 |
| Fibroblastic | 10 | 6 | 60 |
| Psammomatous | 4 | 2 | 50 |
| Secretory | 1 | 1 | 100 |
| Microcystic | 3 | 2 | 66.66 |
| Angiomatous | 5 | 2 | 40 |

**Table 3: Association between PR status and MIB1 Labelling Index**

| PR Status | No. of cases | MIB 1 LI | |
|---|---|---|---|
| | | Mean MIB1 LI | SD |
| Positive | 63 | 1.11 | 0.63 |
| Negative | 37 | 3.84 | 7.22 |

**Figures:**

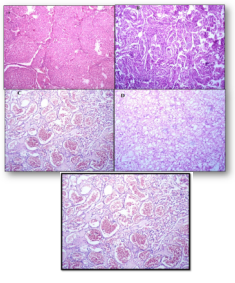

**Figure 1** Histology of Grade 1 meningioma variants, (A) Meningothelial meningioma showing uniform tumor cells arranged in lobules (B) Transitional meningioma showing well defined whorls. (C) Angiomatous meningioma dominated by excessive vascularization. (D) Microcystic meningioma showing numerous small microcysts ( A-D Haematoxylin and Eosin, X100).

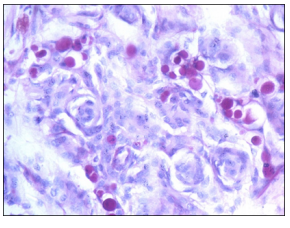

**Figure 2:** Secretory meningioma showing numerous PAS positive pseudopsammoma bodies( Periodic Acid Schiff[PAS] stain, X400).

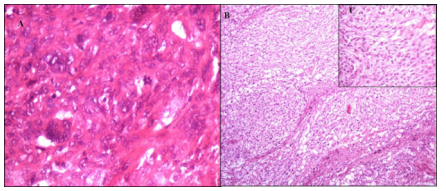

**Figure 3:** Figure 3(A) Atypical meningioma (Grade II) showing pleomorphism and atypical mitotic activity (Haematoxylin and Eosin, X400).(B) Clear cell meningioma showing a pattern less tumor dominated by cells with clear cytoplasm (Haematoxylin and Eosin, X100) (C) Clear cell meningioma high power (Haemotoxylin and Eosin, X400).

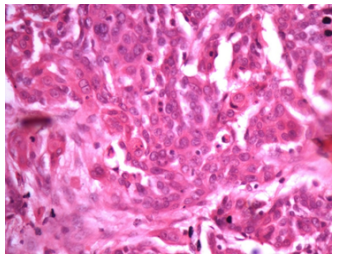

**Figure 4:** Anaplastic meningioma (Grade III) showing high mitotic activity (Haematoxylin and Eosin, X400).

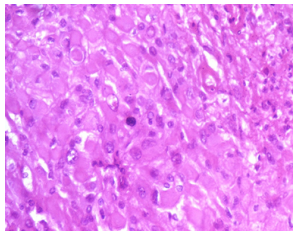

**Figure 5:** Rhabdoid meningioma showing sheets of cells with eccentrically placed vesicular nuclei, prominent nucleoli and prominent inclusion like eosinophilic cytoplasm (Haematoxylin and Eosin X400)

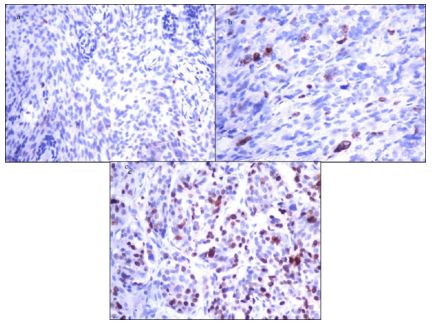

**Figure 6(a)** Grade I Meningothelial meningioma showing low Ki-67 expression with occasional brown stained nuclei (X400)(b) Atypical Meningioma (Grade II) showing moderate expression of Ki-67 (X400)Figure (c) Anaplastic meningioma (Grade III) showing high Ki-67 expression (X400)

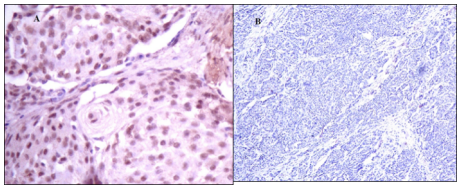

**Figure 7:** (A) Grade I Meningioma showing strong PR expression (X400).Figure 7(B) Anaplastic meningioma (Grade III) showing absence of PR expression (X100)

**References:**

1.Kumar S, Kakkar A, Suri V, Kumar A, Bhagat U, Sharma MC et al.

VOLUME - 4 | ISSUE - 1 | January - 2020 | ISSN (O) : 2663-2888 | ISSN (P) : 2663-287X

Evaluation of 1p and 14q status, MIB-1 labeling index and progesterone receptor immunoexpression in meningiomas: Adjuncts to histopathological grading and predictors of aggressive behavior. Neurol India 2014;62:376-82.
2. Perry A, Louis DN, Budka H, Von DA, Sahm F, Rushing EJ. Menigioma. In: Louis DN, Ohgaki H, Weitmer OD, Cavenee WK Editors. WHO Classification of Tumors of the Central Nervous System. Revised 4th edition. Lyon: IARC; 2016. 232-245.
3. Perry A, Louis DN, Scheithauer BW, Budka H, von Deimling A. Meningiomas. In: Louis DN, Ohgaki H, Wiestler OD, Cavanee WK. World Health Organization Classification of Tumors of the Central Nervous System. 4 th ed. Lyon: IARC; 2007. 164-172. 4. Shayanfar N, Mashayekh M, Mohammadpour M. Expression of progestrone receptor and proliferative marker Ki 67 in various grades of meningioma. Acta Med Iran 2010;48:142-7.
5. Kayaselcuk F, Zorludemir S , Bal N, Erdogan B, Erdogan S, Erman T. The expression of survivin and Ki-67 in meningiomas : Correlation with grade and clinical outcome. J Neurooncol 2004;67:209-214.
6. Abramovich CM, Prayson RA. MIB-1 labelling indices in benign, aggressive , and malignant meningiomas: A study of 90 tumors. Hum Pathol 1998;29:1420-27
7. Amatya VJ, Takeshima Y, Sugiyama K, Kurishu K, Nishisaka T, Fukuhara T et al. Immunohistochemical Study of Ki-67(MIB-1), p53 Protein , p21, and p27 expression in Benign, Atypical, and Anaplastic Meningiomas . Hum Pathol 2001;32:970-75.
8. Karamitopoulou E, Perentes E, Tolnoy M , Probst A. Prognostic significance of MIB-1, p53,and bcl2 Immunoreactivity in meningiomas. Hum Pathol 1998;29:140-145
9. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol 2004;57:1033-37
10. Perry A, Cai DX, Scheithauer BW, Swanson PE, Lohse CM, Newsham IF, Weaver A, Gutmann DH. Merlin, DAL-1, and progesterone receptor expression in clinicopathologic subsets of meningioma: a correlative immunohistochemical study of 175 cases. JNeuropathol Exp Neurol 2000; 59:872-79.
11. Hsu DW, Efird JT, Hedley Whyte ET. Progesterone and estrogen receptors in meningiomas: prognostic considerations. J Neurosurg 1997;86:113-20.
12. GursanN, Gundogdu C, Albayrak A, Kabalar ME. Immunohistochemical detection of progesterone receptors and the correlation with Ki-67 labeling indices in paraffin-embedded sections of meningiomas. Int J Neurosci. 2002; 112:463-70.
13. Nagashima G, Aoyagi M, Wakimoto H, Tamaki M, Ohno K, Hirakawa K. Immunohistochemical detection of progesterone receptors and the correlation with Ki-67 labeling indices in paraffin-embedded sections of meningiomas. Neurosurgery 1995;37:478-83.
14. Brandis A, Mirzai S, Tatagiba M, Walter GF, Samii M, Ostertag H. Immunohistochemical detection of female sex hormone receptors in meningiomas: correlation with clinical and histological features. Neurosurgery 1993;33:212-21.
15. Bruna J, Brell M, Ferrer I, Gimenez-Bonafe P, Tortosa A. Ki-67 proliferative index predicts clinical outcome in patients with atypical or anaplastic meningioma. Neuropathology 2007;27:114-20.
16. Ohba S, Kobayashi M, Horiguchi T, Onozuka S, Yoshida K, Ohira T, et al. Long-term surgical outcome and biological prognostic factors in patients with skull base meningiomas. J Neurosurg 2011;114:1278-87
17. Skender-Gazibara M, Cvetkovic-Dozic D, Dozic S, Govedarovic V. Value of the proliferative and hormonal markers in estimation of biological behaviour of meningioma. Arch Oncol 2002;10:182-3..
18. Ruiz J, Martínez A, Hernández S, Zimman H, Ferrer M, Fernández C, et al. Clinicopathological variables, immunophenotype, chromosome 1p36 loss and tumor recurrence of 247 meningiomas grade I and II. Histol Histopathol 2010;25:341-9
19. Christensen HC, Kosteljanetz M, Johansen C. Incidences of gliomas and meningiomas in Denmark, 1943 to 1997. Neurosurgery 2003;52:1327-34.
20. Klaeboe L, Lonn S, Scheie D, Auvinen A, Christensen HC, Feychting M, et al. Incidence of intracranial meningiomas in Denmark, Finland, Norway and Sweden, 1968-1997. Int J Cancer 2005; 117:996-1001.
21. Cordera S, Bottacchi E, D'Alessandro G, Machado D, De Gonda F, Corso G. Epidemiology of primary intracranial tumours in NW Italy, a population based study: stable incidence in the last two decades.J Neurol 2002;249:281-84.
22. Willis J, Smith C, Ironside JW, Erridge S, Whittle IR, Everington. The accuracy of meningioma grading: a 10-year retrospective audit. Neuropathol Appl Neurobiol 2005;31:141-49.
23. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol 1997;21:1455-65.
24. Maier H, Ofner D, Hittmair A, Kitz K, Budka H. Classic, atypical, and anaplastic meningioma: three histopathological subtypes of clinical relevance. J Neurosurg 1992;77:616-23.
25. Jaaskelainen J, Haltia M, Servo A. Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. Surg Neurol 1986;25:233-242.
26. Mukherjee S, Ghosh SN, Chaterjee U, Chaterjee S. Detection of progesterone receptor and correlation with Ki-67 labelling index in meningiomas. Neurol India 2011;59:817-822.
27. Langford LA, Cooksley CS, DeMonte F. Comparison of MIB-1 (Ki-67) antigen and bromodeoxyuridine proliferation indices in meningiomas. Hum Pathol 1996;27:350-54.
28. Striepecke E, Handt S, Weis J, Koch A, Creerius U, Reineke T, et al. Correlation of histology, cytogenetics and proliferation fraction (Ki-67 and PCNA) quantitated by image analysis in meningiomas. Path Res Pract 1996; 192:816-24.
29. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. The prognostic significance of MIB-1, p53, and DNA flow cytometry in completely resected primary meningiomas. Cancer 1998;82: 2262-69.
30. Perry A, Scheithauer BW, Stafford SL, Lohse CM, Wollan PC . "Malignancy" in meningiomas: a clinicopathologic study of 116 patients, with grading implications. Cancer 1999;85:2046-56.