International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.9, pp 899-904, 2017

The Correlation of Ki-67 Labeling Index in Prognostic of Meningiomas

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Abstract : Meningiomas are benign tumor that have the highest prevalence among primary brain tumor. The incidence in women is approximately twice than in men. Ki-67 associated with his to logical grade and risk of recurrent meningioma. Aims of this study isto know the relationship between the level of cell proliferation was assessed by Ki-67 staining on the prognosis of meningioma.
Materials and methods : Analytic cross sectional research of 63 paraffin-embedded sections of meningiomas were collected. Entire blocks of paraffin meningioma specimens that had previously been performed hematoxylin-eosin staining base and confirmed as ameningiomaper for medimmunohistochemical staining of Ki-67. After staining, calculated labeling index (LI) ofKi-67 staining.Ki-67 status was also defined into three groups as no proliferation, low proliferation (< 14%), and high proliferation (> 14%).
Results : The number of mitotic measured based on the classification of meningioma was found that the majority of meningiomas grade 1 hasa weak degree of mitosisin the amount of 56 samples(88.9%). While meningiomas grade 2 has a strong degree of mitosis that is equal to7 samples(11.1%). Out comes obtained inpatients with IHC weak meningioma showed better results which amounted to48%. Where as patients with meningioma showed strong IHC bad outcomes which amounted to15%. Of the entire specimen sample, only 43/63 specimens that expressonly staining observed in meningioma grade I. The calculation of the relationship betweenKi-67 LI staining with computerized meningioma prognosis with Chi-square statistical test($p < 0.05$) to obtain$p=0.758$.
Conclusion : There was nosignificant relationshipbetweenKi-67 staining Labeling index with the prognostic of patients with meningioma. This study found staining of Ki-67 LI strong on twenty samples of meningioma grade I.
Key words : Meningioma, Ki-67 antigen, Labelling Index.

Introduction

Meningioma is a benign tumor of meningens that grows from arachnoid cap cells that are derived from arachnoid villi. Meningioma is the most commonly diagnosed primary brain tumor of 33.8% of all primary brain tumors. In the United States, the incidence of meningioma with a confirmed pathological examination is estimated at 97.5 per 100,000 inhabitants. However, this amount is estimated to be lower than the real amount due to the presence of some non-surgical meningiomas. In the UK, the incidence of meningioma is estimated at 5.3 per 100,000 people and has remained stable over the past 12 years.[1,2]

Some risk factors for meningioma are age, radiation exposure, genetic and hormonal. Meningioma incidence increases with age with the peak at age 40 to 60 years. The incidence of meningioma in women is twice as high as in men. In the UK, the incidence of meningioma in women is 7.19 per 100.00, while in men is 3.05 per 100.00 per year. It is not much different in America, the incidence of meningioma in women is twice that of men, 8.36 and 3.61 per 100,000 for women and men. This suggests a possible link between meningioma and sex hormones.[1,2]

Research shows that the use of sex hormone therapy increases the risk of meningioma in postmenopausal women significantly. Other studies have shown a decreased risk of meningioma in menopausal women. In women who have been pregnant also experienced a decrease in the risk of meningioma and stronger along with the increase number of pregnancies.[1,3]

Recent studies have shown that mitosis in meningioma is affected by several receptor proteins, such as Epidermal Growth Factor, Granulin, Platelet Derived Growth Factor, Vascular Endothelial Growth Factor, Insulin Growth Factor, Fibroblast Growth Factor and progesterone and estrogen hormones. The mechanism of increased proliferation of meningioma cells varies depending on the type of receptor being stimulated. One of the process of increasing proliferation is through stimulation of DNA synthesis in the nucleus of meningen cells.[4]

Ki-67 is associated with higher hystological grade and an increased risk of recurrent meningioma. The average LI in benign meningioma was 3%, for atypical meningioma of 8% and for malignant meningioma of 17%. Most studies reported a higher proliferation index in recurrent meningiomas compared with non-recurrent ones. Meningioma with MIB-1 index of 4% or more significantly has a higher tendency to recurrence. Ki-67 has also been reported to be higher in males compared with women and in meningiomas with edema in MRI. Ki-67 is lower in meningioma with calcification. Meningiomas associated with NF-2 have higher LI than sporadic ones and this reflects the more aggressive nature of these meningiomas.[5]

Research has investigated the possibility of prognostic factors in atypical and malignant meningiomas in particular. In an analysis of 76 atypical meningiomas and 10 malignant meningiomas, the number of high mitosis, brain invasion, and parasagittal-falcine sites was significantly associated with a reduction in recurrence-free survival.[6] Also, the Ki-67 index greater than 4% was also associated with a decrease Time to relapse. This appears to be an important pathological indicator of the aggressiveness of this type of tumor.

In Indonesia there is no research on the relationship between Labeling Ki-67 Index with the prognosis of Meningioma so that new ideas are going to be needed to develop the results of this study.

Based on this, researchers are interested to examine the relationship between Ki-67 Labelling Index on the prognosis of meningioma patients with hope that the knowledge about the nature of meningioma can be implications in the determination of prognosis and treatment of meningioma in the future.

Methods

This research uses observational research method is cross sectional analytic. The study was conducted at RSUP.H. Adam Malik Medan and anatomical pathology laboratory of RS.Pirngadi, Medan, North Sumatra, was conducted from May to August 2014. The study sample was performed in August 2014. Data were taken from patients with intracranial and spinal meningiomas who had undergone tumor removal surgery at RSUP. H. Adam Malik Medan since 2010 with histopathological examination of tissue according to the description of meningioma assessed survival for 2 years. Inclusion criteria of this study were patients with intracranial meningioma who had surgery with histopathologic results in accordance with the description of meningioma. While Patients with signs of hormonal disturbance along with other systemic diseases such as diabetes mellitus, kidney and liver disease and other tumor diseases are included in the exclusion criteria. The patient data of the research sample were collected and recorded based on the patient's medical record. Data recorded include gender, age, tumor location, grade by WHO, and histopathology type.

Result

Sex Distribution

Data collection of research showed that the percentage of female meningioma patients is 71,4% and male is 18 patient (28,6%). Table 1 shows that female suffers meningioma more than men with a ratio of 2:1.

Table 1. Distribution by sex		
Sex	**N**	**%**
Male	18	28,6
Female	45	71,4
Total	63	100.0

Age Distribution

The analysis of this study sample by age provides a mean value of 43.04 years (SD ±10,66) with an age range of 19 years to 75 years. The median value is 43 years. In the age group table, it was found that the highest incidence of meningioma is in age group of 41 - 50 years which was 22 cases (34.9%). While the frequency of occurrence is least found in the <20 years age group and 71-80 years which is 1 case (1.6%).

Table 2. Descriptive Analysis of Age

Ages Group (years)	**N**	**%**
<20	1	1,6
21 – 30	7	11,1
31 – 40	20	31,7
41 – 50	22	34,9
51 – 60	10	15,9
61 - 70	2	3,2
71- 80	1	1,6
Total	63	100.0

	Value
Mean	43,04
Median	43
Std. Deviation	10,66
Minimum	19
Maximum	75

Distribution of WHO grading

The most common type of meningioma based on WHO classification in this study were benign type which was 56 cases (88,9%). It is followed by atypical type with 5 cases (7.9%) and anaplastic with 2 cases (3.2%).

Table 3. Distribution of WHO grading

WHO Grading	N	%
Benign	56	88,9
Atypical	5	7,9
Anaplastic	2	3,2
Total	63	100.0

Distribution of Histopathological Type

In this study, the most common histopathology type of meningioma was meningothelial meningioma with 28 cases (44.4%), followed by fibroblastic meningioma with 14 cases (22.2%) and transitional meningioma with 7 cases (11.1%), contrary, the least common type is secretory meningioma and clear cell meningioma with 1 cases (1.6%)

Table 4. Distribution of Histopathological Type

Histopathological Type	N	%
Meningothelial	28	44,4
Fibroblastic	14	22,2
Psammomatous	4	6,3
Transitional	7	11,1
Secretory	1	1,6
Atypical Angiomatous	4 2	6,35 3,2
Anaplastic Clear cell	2 1	3,2 1,6
Total	63	100.0

Distribution of Ki-67 Labelling Index by Meningioma Classification

The number of mitoses which was measured using Ki-67 labelling index is analyzed by the classification of meningioma. It was found that the majority of grade 1 and 2 meningiomas had weak mitosis with 43 samples (68.3%) and 5 samples (7.9%) respectively. While grade 1 and 2 meningioma had a strong degree of mitosis with 13 samples (20.6%) and by 2 samples (3.2%) repectively.

Table 5. Distribution of Ki-67 Labelling index by meningioma classification

Ki-67 Labelling Index	**Grade I Meningioma**	**Grade II Meningioma**	**Total**
Weak(< 14,7% /10 LPB)	43	5	48
Strong(≥ 14,7 % /10 LPB)	13	2	15
Total	56	7	63

Correlation of Ki-67 Labelling Index and Outcome of Patient

Outcomes obtained in patients with meningiomas with weak IHC showed better prognosis of 48%. While meningioma patients with strong IHC showed a poor outcome of 15%.

Tabel 6. Distribution of Outcome by Labelling Index

		Outcome		Total
		Survive	Death	
Ki-67 Index	Strong	10	5	15
	Weak	39	9	48
Total		49	14	63

Discussion

Meningioma is a benign tumor that occurs in the central nervous system brain membrane derived from the neuroektodermal layer that forms the arachnoid cap cells that form the outer layer of the arachnoid membrane and the arachnoid villi. These tumors account for about 20% of all intracranial primary tumors with reported incidents of 4.4 per 100,000 people per year and are diagnosed in the average 63-year-old patient.[7]

Epidemiological studies show that dominant meningioma occurs in women than men with a ratio of 2: 1. This study shows that there is a higher incidence of meningioma incidence in women than in men.[6]

The results of this study showed that the division of meningioma patients based on gender are women as many as 45 people (71.4%) and men 18 people (28.6%). The table shows that female suffers meningioma more than men with a ratio of 2:1. Based on epidemiological studies, the incidence of meningioma increases with age with peak incidence at age between 40-60 years.[8] In the age group table it was found that the highest incidence of meningioma in age group 41 - 50 years was 22 cases (34.9%). While the frequency of occurrence was found least in the <20 years and 71-80 years age group which is 1 case (1.6%)

Meningioma grade I is the most common type found in the United States and Britain with an estimated between 90-95%. Based on the histopathologic type it is found that meningothelial, fibrous and transitional meningiomas are the most common type. This indicates the presence of the same type of meningioma incidenceinthisstudy.[9]

The classification of meningioma based on WHO grade showed that the most frequencies were benign meningioma type which was 56 (88,9%) cases. Then followed by atypical as many as 5 cases (7.9%) and anaplastic as much as 2 cases (3.2%).

The number of mitoses measured by the classification of meningioma found that the majority of grade 1 and 2 meningiomas had weak mitosis of 43 samples (68.3%) and 5 samples (7.9%). While grade 1 and 2 meningioma had a strong degree of mitosis of 13 samples (20.6%) and by 2 samples (3.2%)

Outcomes obtained in patients with meningiomas with weak IHC showed better results of 48%. While meningioma patients with strong IHC showed a poor outcome of 15%.

Conclusion

This study found 63 cases of meningioma in RSUP. H. Adam Malik Medan in the period of research that is four years with age average of 43,04 (SD 10,66) year with age range 19 years until 75 years old. Meningioma classification based on WHO grade showed that most frequencies were benign meningioma type which was 56 (88,9%) cases. Then followed by atypical as many as 5 cases (7.9%) and anaplastic as much as 2 cases (3.2%). Meningioma classification based on hystopathology type of most frequency tumors was meningothelial meningioma of 28 (44.4%) cases, fibroblastic meningioma 14 (22.2%) cases followed by transitional meningioma 7 (11.1%) cases, and the most rare was Secretory meningioma and clear cell meningioma of 1 (1.6%) cases. The number of mitoses measured by the classification of meningioma found that the majority of grade 1 and 2 meningiomas had weak mitosis of 43 samples (68.3%) and 5 samples (7.9%). While grade 1 and 2 meningioma have strong degree of mitosis that is 13 samples (20.6%) and 2 samples (3.2%).

Of the total specimen samples, only 43/63 specimens expressing staining were found only in grade I meningioma. The calculation of the association between LI Ki-67 staining and computerized meningioma prognosis with Chi square test ($p < 0.05$) obtained $p = 0.758$. This shows that there is no significant relationship between ki-67 labeling index with the prognosis of patients with meningioma. This study found strong LI Ki-67 dyeing in twenty samples of grade I meningioma.

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