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The Correlation of KI-67 Labeling Index With WHO Histopathological Grading in Intracranial Astrocytoma Patients at Haji Adam Malik Hospital Medan

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Abstract : Introduction.Ki-67 is an excellence marker to determine the cell proliferation and it can be very helpful when there is a discrepancy between clinical parameters and histopathological result. In indonesia, no previuously study correlating the Ki-67 labeling index and WHO astrocytoma histophatological grade has done.
Aims.To determine the correlation of cell proliferation by using the Ki-67 and the WHO classification for intracranial astrocytoma.
Method.This study was conducted using an analytic cross sectional study and sample was taken using total sampling technique, all specimens from astrocytoma patients whom undergo tumor removal from January 2014 – June 2015. All astrocytoma paraffin specimens which has stained using hematoxyline-eosine and confirmed as an astrocytoma was collected dan patients data was recorded. Ki-67 staining was done to all specimens. The precentage of staining tumor cell nucleus was count. To examine the correlation of cell proliferation by using the Ki-67 then the data analized using the *Chi-square* statistical test. P value $\leq$0,005 considered to be a significant correlation. While p value >0,05cosidered to be a not significant correlation.
Result. There were no significant correlation of Ki-67 precentation and intracranial astroctyoma classification, (p = 0,076).
Conclusion. The insignificant result incongruent with the previously studies which conclude that there was a significant correlation of Ki-67 and astrocytoma classification. The insignificant result maybe because the data doesn't distributed normally.

Introduction

Astrocytoma is a major part of glioma (> 75%) and diffuse infiltrating astrocytoma accounts for 60% of all primary brain tumors. Glioma alone accounts for half of all primary brain tumors with low grade glioma covering 15% of all brain tumors in adults and represents 25% of all brain tumors in children. Glioma is a neuroectodermal tumor derived from sustentacular neuroglia cells.[1,2]

Astrocytoma is divided into 4 grades in the WHO classification. It is important to distinguish grade 2 and grade 3astrocytomas because it greatly differentiates the management and prognosis of the patient. The WHO classification is based on the proliferative activity of the neoplastic cells found.[3]

Low grade astrocytoma is grade 2 astrocytoma according to WHO classification and grade 1 and 2 astrocytoma according to Kernohan Grading system. High grade astrocytomas or malignant astrocytomas

include anaplastic astrocytoma which are the third grade of WHO classification and glioblastoma multiforme and gliosarcoma which are the fourth degree of WHO classification .[1,4]Glioblastoma Multiforme is the most malignant primary brain tumor, constituting 15% of all intracranial tumors and 50-60% of astrocytic tumors.[5]

Difficulty is often found when determining grade 2 or grade 3 astrocytoma based on WHO classification. As in the case where histopathologyshows a low grade astrocytoma but has clinical and radiological manifestations in the direction of malignancy or vice versa which histopathology shows high gradeastrositoma but clinically and radiologically does not lead to malignancy.[6]

Studies have demonstrated a positive correlation between Ki-67 and grade of tumors based on the WHO classification.[3] Ki-67 is rated as the best marker for assessing tumor cell proliferation and may be helpful in cases like this where histopathology shows low grade astrocytoma whereas other parameters are more inclined towards malignancy.

The proliferation index is a potent marker that can estimate the growth of neoplasms quantitatively and is useful for determining prognosis in patients with neoplasms. Various methods have been used to estimate the proliferation index in central nervous system tumors and from these various methods, the most potent method is by Ki-67 labeling index.[6] Ki-67 is quantitatively associated with mitotic index by distinguish cell cycle time difference.[7] Ki-67 proved to have diagnostic and prognostic value in astrocytic tumors.[8] Expression of Ki-67 was proportional to WHO classification.[9]

The expression of Ki-67 and p53 gene on pilocytic astrocytoma and diffuse astrocytoma was significantly lower than that of high grade astrocytomas. However, no significant difference in expression between pilocytic astrocytoma and diffuse astrocytoma. Ki-67 is said to be a better marker for distinguishing astrocytoma grades as well as for determining outcome in patients compared with p53.[10]The relevance between prognosis and p53 expression is also debatable.[11]

In Indonesia, studies relating Ki-67 labeling index with astrositoma degree have not been done so it is not known whether the role of Ki-67 is very helpful in determining the grades and prognosis as has been suggested in previous studies also in accordance with the population of astrocytoma patients in Indonesia. Therefore, researchers interested to examine the relationship between Ki-67 labeling index with WHO classification of astrocytoma.

Material and Method

This research uses cross sectional analytic research method that is intended to analyze the relationship between proliferation rate of Ki-67 with grade of astrocytoma. This study used a total sampling technique, that is all specimens from astrocytoma patients who had undergone tumor removal surgery in January 2014 - June 2015 with histopathological examination results of an astrocytoma. In that period, there were 25 samples of astrocytoma.

All specimens that had previously been subjected to hematoxylin-eosin-based staining and confirmed as an astrocytoma from January 2014 to June 2015 were collected.Patient data such as gender, age, and WHO grade are recorded. Ki-67 immunohistochemical staining was performed on all collected specimens. After staining Ki-67, it is calculated how much percentage of tumor cell nuclei that stained.

The data obtained will be processed using data processing software. Categorical variables are analyzed in terms of frequency and percentages presented in tabular form. Descriptive analysis of numerical variables is concentration (mean, median) and spread (standard deviation, minimums). If the data distribution is normal, mean and standard deviation are used. If the data distribution is abnormal, median is used with minimum and maximum values.

Medical and demographic data of name, sex, age, WHO grade of astrocytoma,specimens number, and outcome were computerized by Chi-square statistic test. P value of 0.05 is considered to be a significant relationship. While the P value> 0.05 is considered there is no significant relationship.

Result

In this study, 25 samples of patients with intracranial astrocytoma was obtained. Of the 25 samples, 10 are female and 15 are male with ratio of 1: 1.5. Patient age ranges between 40-49 years (32%) with median 37, the youngest are 9 years old and the oldest are 68 years old.

In this study, grade I astrocytoma a is the most common type of astrocytoma that is equal to 36%, followed by grade II and grade IV respectively by 24%, and grade III of 14%.

To see if the percentage of Ki-67 also had a role in astrocytoma classification, Spearman test was performed with p = 0.076 (p> 0,05). This shows that there is no significant correlation between percentage of Ki-67 with the grade of astrocytoma.

In this study, from 25 patients, 18 patients islive and 7patiets died. In weak Ki-67 staining group , 7 patients is live and 7 patients died, whereas in strong Ki-67 staining group, 9 patients is live and 5 patients died. Two patients with negative Ki-67 staining results, both live. To see whether the percentage of Ki-67 also had a role in the prognosis in this study, Chi-square test was performed with p = 0,512 (p> 0,05). This suggests that there is no significant relationship between the percentage of Ki-67 and the prognosis of the patient.

Table 1. Ki-67 labeling index Distribution to Astrocytoma Classification

Ki-67	Grade I atsrocytoma	Grade II atsrocytoma	Grade III atsrocytoma	Grade IV atsrocytoma	p
Negative	11,1%	0,0%	25,0%)	0,0%	
Weak (≤ 10 %)	66,6%	16,6%	0,0%	33,3%	0,076*
Strong (> 10 %)	22,2%	83,3%	75,0%	66,6%	
Total	100%	100%	100%	100%	

*Spearman

Table2. Ki-67 labeling index Distribution to Outcome

Ki-67	Live	Die	Total
Negative	100%	0%	8%
Weak(≤ 10%)	77,7%	22,2%	36%
Strong(>10%)	64,2%	35,7%	56%
Total	72%	28%	100%

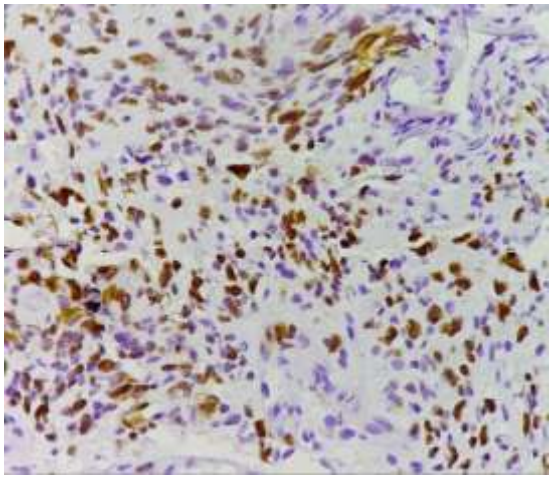

Figure 1.Strong Ki-67Staining(> 10%).

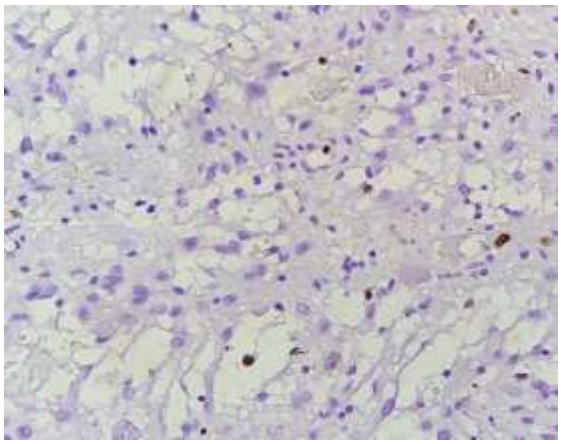

Figure 2.Weak Ki-67Staining(≤ 10%).

Discussion

In this study, the comparison of male and female patients is 1.5: 1. In 2014 Thotakura through his study described the same thing that the incidence of astrocytoma is more prevalent in males than in females with male: female ratio = 1.84: 1.[6]This supports the previous literature that more astrocytoma are found in men than in women. High grade astrocytoma in women is more common in menopausal age so there is speculation that female hormones have a protective effect on astrocytoma.[1]

The high incidence of males compared to females did not have an impact on Ki-67 levels where in patients with weak Ki-67 staining there are 5 male and 4 female patients, whereas in patients with strong Ki-67 staining there are 8 male patients and 6 female patients. Analysis on the data has performed and the result is p value = 0.483. This means there is no significant difference between the levels of Ki-67 in women and men. Ki-67 levels are not influenced by gender.

Highest incidence of astrocytoma isbetween 40-49 years (32%) with median 37, the youngest is 9 years old and the oldest is 68 years old. Previously in 2014,Thotakura suggests a similar thing where their study found the highest number of astrocytoma events found in the fourth and fifth decade that includes 49.52 of the entire sample.[6]

In this study found that grade I astrocytoma is the most common type of astrocytoma that is equal to 36%, followed by grade II and grade IV respectively by 24%, and grade III of 14%. This result does not resemble previous studies where the highest incidence was found in grade II astrocytoma for 39.9% followed by grade IV astrocytoma for 36.2%, grade III astrocytoma for 14.3% and grade I astrocytoma for 9.5% .[8] Publication by Johannessen et al. explained that the percentage of Ki-67 is increasing along with thegrade of WHO classification. This is because Ki-67 can assess the proliferation activity of tumor cells so that a high Ki-67 percentage shows a more malignant tumor.[12]From a study conducted by Thotakura in 2014 similar results were also found.[6]

Differences in Ki-67 values between low grade and high grade astrocytoma according to some previous studies was vary.[6] Ki-67 values above 10% are considered appropriate to be a reference indicating that an astrocytoma has the potential to be malignant.[12] Therefore in this study the assessment of Ki-67 values is differentiated to <10% and> 10%. In this study, Spearman test was done to see whether the percentage of Ki-67 also has role in astrocytoma classification with p = 0,076 (p> 0,05). This shows that there is no significant correlation between percentage of Ki-67 with intracranial astrocytoma classification. This is not in accordance with previously published publications which conclude that there is a significant relationship between Ki-67 and the degree of astrocytoma classification. The absence of a significant relationship may be becausethe data not normally distributed.

In 1994, Sallinen concluded that the best sensitivity and specificity was found in Ki-67 percentage of 8% and Ki-67 was characterized as having the potential to assess a strong prognosis with 15.3% as a limit. In a study conducted by Di et al in 1997 concluded that the Ki-67 score <8% was associated with better prognosis of

either 5 or 10 years. In a study conducted by Reavey-Cantwell in 2001, it was found that patients with astrocytoma with a Ki-67> 20% value had a 2.2 times greater risk of death than patients with a Ki-67 <20% . All of these publications support that Ki-67 has a prognostic value for both safety and recurrence.[12]

This study showed that there was no significant relationship between the percentage of Ki-67 and the prognosis of the patients (p = 0,512). This is not in accordance with previous publications which conclude that there is a significant relationship between Ki-67 and the prognosis of patients with astrocytoma.[6]

Conclusion

There was no significant correlation between proliferation index based on Ki-67 value with WHO classification of astrocytoma with p = 0,076 (p> 0,05). There was no correlation between proliferation index based on Ki-67 value and prognosis of astrocytoma patients,p = 0,512 (p>0,05)

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