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Relations between KI-67 immunohistochemistry expression with histopathology grading and prostate-specific antigen (PSA) values in adenocarcinoma prostate at Dr H. Adam Malik Hospital, Medan Indonesia

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ABSTRACT

Background: The degree of proliferation of a tumor is closely related to the biological behavior of these tumors, there is research showing over-expression of Ki-67 in prostate adenocarcinoma that associated with increased histopathology grading which showed an aggressive tumor.

Objective: The aim of this study was to determine the relations between Ki-67 immunohistochemistry (IHC) expression with histopathology grading and PSA values in prostate adenocarcinoma patients at Dr. H. Adam Malik Hospital. Methods: This study is a cross-sectional analytic study. The research was carried out in Division of Urology and Pathology Anatomy of Medicine Faculty of Sumatera Utara University at Dr. H. Adam Malik Hospital.

Results: In this study, it was found that over-expression of Ki-67 as many as six patients (40%) in grade group 2 (3 + 4 = 7), while as many as 15 patients (100%) with low-expression of Ki-6. In this study, it was found over-expression of Ki-67 as many as six patients (40%) in the Gleason Score 7 to the degree of moderately differentiated histology, while as many as 15 patients (100%) on the Gleason Score ≤6 well-differentiated histology degrees with low-expression of Ki 67.

Conclusion: There is a significant correlation between expression of Ki-67 IHC with histopathology grading adenocarcinoma of the prostate (p> 0.05). There is no significant relationship Expression of Ki-67 IHC with PSA values in prostate adenocarcinoma (p <0.05).

Keywords: prostate cancer, adenocarcinoma, Ki-67 IHC

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BACKGROUND

The prostate cancer incidence rate in Indonesia is also increasing every year.[1] The incidence of prostate cancer in Indonesia is often at the age above 60 years and rarely at the age under 40 years.[1] Prognostic and predictive factors in prostate cancer can be judged from the clinical and biological aspects. TNM staging, PSA levels, and Gleason scores were prognostic marker that was commonly used, but with a growing knowledge of molecular biology, the concept of oncogenesis, tumor suppressor genes dominate tumor genesis research, evaluation of gene and protein provide new prognostic markers such as Ki-67.[2]

Ki-67 is an antigen that expressed by the cell nucleus when cells are dividing themselves. At the time the cells divide, the new DNA will also be formed with a long DNA template based, at which time the synthesis process will express the Ki-67 antigen. Ki-67 is expressed in the cell cycle in the S-phase, G1, G2 and M phases but it is not found in the G0 phase.[3] It has proof that Ki-67 expression is found in the state of prostate cancer and benign prostatic hyperplasia (BPH), but the levels of Ki-67 were more found in cancerous prostate condition.[2,3]

Prostate Specific Antigen (PSA) is a serine protease that produced by the ductal and acinar epithelium of the glands from normal cells, hyperplasia and malignant prostate tissue. Because of the influence of pathological processes in which the integrity of the damaged cells will cause an increase in the value of PSA which will then be entered into the circulation, such as hyperplasia, inflammation, tumor where this is all leading cause an increase in the PSA values. Research has shown that every gram of prostate cancer tissue will increase the average PSA values of 2.3 ng / ml.[4] Increased PSA values assessed by histological characteristics of epithelial cells in PSA neoplastic serum process improvement depends on the differentiation of tumor cells.

There are several systems in determining the degree of malignancy of prostate cancer, and the most common are the Gleason system which was

one of the grading systems.[5] Basis of Gleason's system represented by five histological which uses microscopic picture, gland architecture analysis, the degree of glandular differentiation and invasion of connective tissue, but not the degree of anaplastic core.[6]

The degree of proliferation of a tumor is closely related to the biological behavior of these tumors. There is research that showing over-expression of Ki-67 in prostate adenocarcinoma is associated with increased histopathologic grading which shows tumor aggressive.[7] Ki-67 levels are associated with recurrences and poor diseases free survival.[8] While PSA affects the pathological process, in which the integrity of the damaged cells will cause an increase in the value of PSA, which will then be entered into circulation. That is why researchers want to see the relationship Ki-67 immunohistochemistry expression with histopathology Grading and PSA value at Dr. H. Adam Malik Hospital.

Table 1 Characteristics of Research Samples

Characteristic	Total	(%)
Ages		
45-55	7	23,3%
56-65	11	36,7 %
66-75	12	40,0%
Grade groups (WHO 2016)		
2-6	20	66,7%
7(3+4)	6	20%
7(4+3)	0	0%
8	1	3,3%
9-10	3	10%
Gleason Scores		
≤ 6	20	66,7%
7	6	20%
8-10	4	13,3%
PSA		
4 – 10	9	30,0%
10,01-20	4	13,3%
20,1-50	8	26,7%
>50	9	30,0%
Ki-67 IHC Expression		
Low-expression	15	50%
Over-expression	15	50%

Table 2 Relations Between Expression of Ki-67 (cut off point 7%) with Grade Group (WHO 2016)

	Ki-67 IHC Expression			
Characteristic	**Low-expression**	**Over- expression**	**Total**	**P value***
Grade Group				
≤ 6	15(100%)	5(33,3%)	20(66,7%)	
7(3+4)	0(0%)	6(40%)	6(20%)	0,001
7(4+3)	0(0%)	0(0%)	0(0%)	
8	0(0%)	1(6,7%)	1(3,3%)	
9-10	0(0%)	3(20%)	3(20,0%)	
Total	15	15	30	

RESEARCH OBJECTIVE

The general objective of this study was to determine the level of relationship Ki-67 immunohistochemistry expression with histopathological grading and PSA values in prostate adenocarcinoma patients at Dr. H. Adam Malik Hospital. The specific objective of this study was to determine the relationship of Ki-67 immunohistochemistry expression with histopathology grading and PSA values in prostate adenocarcinoma patients at Dr. H. Adam Malik Hospital.

METHODE

This study is a cross-sectional analytic study. The research was carried out in Division of Urology and Pathology Anatomy of Medicine Faculty of Sumatera Utara University at Dr. H. Adam Malik Hospital. The study population was patients with treated prostate adenocarcinoma patients in the Division of Urology at Dr. H. Adam Malik Hospital from January 2013 - January 2015. The research was carried out by retrieving data of anatomic pathology patients who had been diagnosed with adenocarcinoma of the prostate and had been examined by PSA values, Gleason scores, and Ki-67 IHC staining.

RESULT

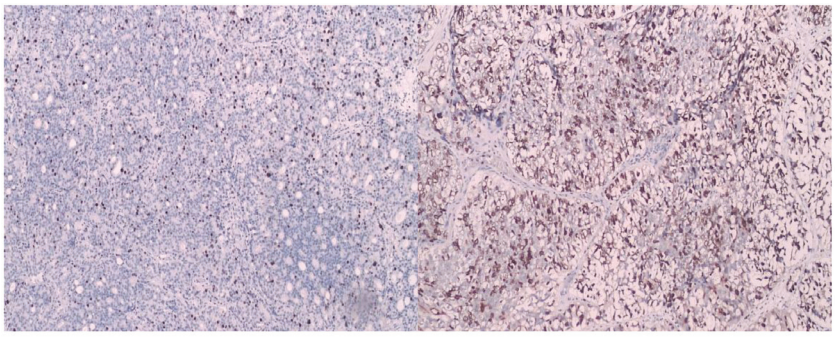
This research was conducted at Dr. H. Adam Malik Hospital to take the data of patients with prostate cancer from 2013 to 2015, obtained 30 samples of prostate adenocarcinoma patients who have met the inclusion and exclusion criteria.

Histopathology Figures of Ki-67

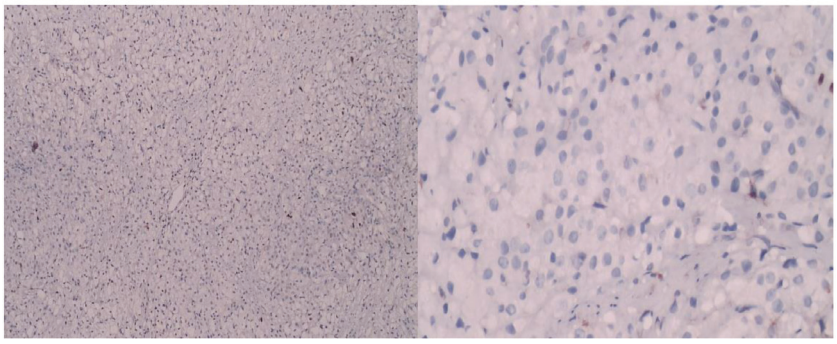
All samples examined by immunohistochemistry of Ki-67, using a mouse monoclonal antibody reagent Ki-67 antigen. After staining, histology obtained as in figure 1.

Distribution of Relations Based on Research Subject Data

Based on histopathological grading that showed in table 1, most respondents are in the 2-6 grading group of 20 patients (66.7%) of the 30 samples, and the fewest respondents are in grading group of 7 (4 + 3) from 0 (0%).



Over-expression of Ki-67,100x Over-expression of Ki-67,400x



Low-expression of Ki-67,100x Low-expression of Ki-67,400x

Figure 1 Expression of KI-67 with IHC staining

Table 3 Relations Between Ki-67 Expression (cut off point 7%) with Gleason Scores

Characteristic	Ki-67 IHC Expression		Total	P value*
	Low-expression	Over- expression		
Gleason Scores				
≤ 6	15(100%)	5 (33,3%)	20(66,7%)	
7	0(0%)	6(40%)	6(20%)	0,001
8-10	0(0%)	4(26,7%)	4(23,3%)	
Total	15	15	30	

Table 4 Relations Between Ki-67 IHC Expression (cut off point 7%) with PSA values

Characteristic	Ki-67 IHC Expression		Total	P value*
	Low-expression	Over-expression		
PSA				
4 – 10	4 (26,7%)	5 (33,3%)	9 (30,0%)	
10,1 – 20	2 (13,3%)	2 (13,3%	4 (13,3%)	0,193
20,1 – 50	2 (13,3%)	6 (40,0%)	8 (26,7%)	
>50	7 (46,7%)	2 (13,3%)	9 (30,0%)	
Total	15 (100%)	15 (100%)	30 (100%)	

Based on 2016 WHO Grade systems group of prostate adenocarcinoma cases with the category of Ki-67 IHC low-expression of encountered more ≤6 grade group of 15 (100%). In contrast to the Ki-67 IHC, over-expression category group mostly grade group of 7 (3 + 4). From the result of analysis using the Fisher exact test showed a significant relationship of adenocarcinoma of the prostate by Grade group with low and over-expression of Ki-67 IHC ($p < 0.05$).

Based on Gleason scores, cases of adenocarcinoma of the prostate with the category of low-expression of Ki-67 IHC encountered more ≤6 grade group of 15 (100%). The degree of well-differentiated histopathology, may not find in the Gleason scores 7 and 8-10, a contrast to the group category over-expression of Ki-67 IHC that more frequent in Gleason scores 6 (40%). Moderately differentiated histopathology degree, at least on the Gleason scores 8-10 with poorly differentiated histopathologic degrees. From the result of analysis using the Fisher exact test showed a significant relationship between Gleason Score of prostate adenocarcinoma with low and over-expression of Ki-67 IHC ($p < 0.05$).

Based on PSA values in table 1. The previous data that showed most was the value of 4-10, and> 50, respectively 30%, while the lowest was the value of 10.1 to 20 which as much as 13.3%.

Based on the PSA group of prostate adenocarcinoma cases with the category of low-expression of Ki-67 IHC encountered more with a value of> 50 as many as 7 (46.7%) followed by grades 4-6 as many as 4 (26.7%) and the lowest with a value> 10, 1-20 and >20.1 to 50 respectively as many as 2 (13.3%). Likewise, the group of prostate adenocarcinoma cases with Ki-67 IHC over-expression category encountered more with a value of> 20.1 to 50 as many as 6 (40%) and the lowest with a value> 10.1 to 20 and> 50 respectively as many as 2 (13.3%). From the result of analysis using X^2 test showed no significant strength in terms of load distribution with low PSA values and high Ki-67 IHC expression ($p > 0.193$).

DISCUSSION

Marker for the growth of a cell can use a protein derived from the cell nucleus; it is Ki-67 proteins.[9] Ki-67 is an antigen that is expressed in the cell nucleus when cells are dividing themselves. At the time the cells divide, the new DNA will also be formed with a long DNA template based, at which time the synthesis process will be expressing the Ki-67 antigen.

If there is no Ki-67 expression in cells that are not dividing and the presence of this protein in tissues that have cleavage, have indicated that this protein plays an important role as a marker of cell division. A number of large-scale studies have confirmed these findings and rarely reported Ki-67 expression in cells that do not divide. Ki-67 genes are on the long arm of human chromosome 10 (10q25).

Ki-67 levels were found in the state of prostate cancer and benign prostatic hyperplasia (BPH), but the higher Ki-67 levels were found in cancerous condition prostate.[2,3] High Ki-67 expression associated with a poor prognosis in prostate cancer patients with a shortening of cancer progression-free survival and cancer specific survival.[9]

In this study, it was found over-expression of Ki-67 as many as six patients (40%) in grade group 2 (3 + 4 = 7), while as many as 15 patients (100%) with low-expression of Ki-6. In this study, it was found over-expression of Ki-67 as many as six patients (40%) in the Gleason scores 7 to the degree of moderately differentiated histology, while as many as 15 patients (100%) on the Gleason scores ≤6 well-differentiated histology degrees with low-expression of Ki-67, this is based on research Madani et al, Ki-67 low-expression of 3 patients (100%) well differentiated, 13 of 21 patients (61.90%) moderately differentiated, and 22 of 25 patients (88%) poor differentiated.[10] Based on the study by Verma et al. in India, from 50 cases of prostate cancer, result in low Ki-67 expression as many as 4 patients (100%) well differentiated, 19-31 (61.29%) moderately differentiated, 13-15 (88.66%) poor differentiated.[2] From the analysis that using Fisher's exact test found a significant relationship between Gleason Score with Ki-67 expression, significant correlation p (0.001) with strong strength of Ki-67 IHC expression with Gleason grading group, as well as research by Sulik M et al found a significant relations between the expression of Ki-67 with Gleason score that high differentiated with p <0,004.[11] Research by Rajeswari K. et al. 2016, of 46 samples showed a significant correlation p <0.05 between Gleason grading system with Ki-67. The combination of both will give strength prognostic value in cancer prostate.[12] It shows that the higher the Gleason grading of tumors, it was according to the higher value of Ki-67 IHC expression. The degree of tumor proliferation is closely linked to the behavior of the biologic tumor is the higher degree of proliferation of the tumor then the more aggressive the tumor. So the prognosis is also getting worse. System Gleason is a grading that useful for determining the prognosis of prostate cancer patients that classify prostate cancer within 5 class with patterns figure based on prostate gland differentiation. The assessment is based on the accumulation of the dominant picture and other features. The higher grade can indicate the level of differentiation that worsens or becomes cancer.[13] Meanwhile, the high levels of Ki-67 expression were associated with high levels of cell proliferation.

Statistical analysis showed that there was no significant association with low PSA levels and high expression of Ki-67 IHC in prostate adenocarcinoma with p> 0.193, the category of low-expression of Ki-67 IHC encountered more with a value of> 50 7 (46.7%). IHC over-expression of Ki-67 encountered more with a value of> 20.1 to 50 6 (40%), while slightly >10-20 and >50 in 2 samples (13.3%), in line with previous research by Sulik M et al showed that low Ki-67 expression in 12 patients (66.7%) with PSA values (4-10) and high expression of Ki-67 of 26 patients (81.3%) with PSA values 10. Therefore, no significant association was found between Ki-67 with PSA values p>0.05. Research Pollack.K.et al. 2002, was obtained from 106 patients, obtained the highest in the low-expression of PSA <10 by 73 (49%), over-expression of PSA> 10 as many as 44 (17%), found that no significant relationship with p> 0.05.

This can be explained that the serum of PSA relates to the size of the tumor, the stage of the pathology that already advanced and a higher degree of the tumor. It is related to the degree of cell proliferation. Although the tumor cells with higher degrees produce less serum PSA compared with low-grade tumors, overall, the tumor with poor differentiation had a higher PSA serum levels because the size of the tumors tends to be larger. But the tumor with a very high degree and poor differentiation would indicate a very low serum PSA, PSA in blood serum have not confirmed the presence of malignancy in man, since PSA is also found in a state of benign tumors.

PSA as a tumor marker is a protein produced by human kallikrein genes. There are about 15 genes have been identified produce kallikrein protein in the human body. Overall these genes produce proteins kallikrein which can be grouped into 3 major groups, namely KLK1 (hK1 or hPRK), KLK2 (hK2 or hGK-1), and KLK3 (hK3 or PSA). In principle, all types of kallikrein can be found in the prostate tissue, but of the three types which have the highest levels within the prostate gland is hK3 or PSA.[14]

CONCLUSION

There is a significant correlation between expression of Ki-67 IHC with histopathology grading adenocarcinoma of the prostate (p> 0.05). There is no significant relationship Expression of Ki-67 IHC with PSA values in prostate adenocarcinoma (p <0.05).

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