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Ki-67 Expression as a Predictive Factor of Muscle Invasion in Bladder Cancer

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Abstract

BACKGROUND: Bladder cancer is the 9th most frequent cancer worldwide. Ki-67 is immunohistochemistry marker that is predictive of cancer cell proliferation. The expression of Ki-67 is associated with poor prognosis in several types of malignancy, yet the value of Ki-67 as the prognostic factor in bladder cancer remains controversial.

AIM: This study is aimed to investigate the association between Ki-67 expression with muscle-invasive bladder cancer (MIBC) and non-muscle invasive bladder cancer (NMIBC).

METHODS: This was a case-control study with a retrospective design. The study was conducted at the Department of Pathology, University of Sumatera Utara, Indonesia. Samples were paraffin blocks from patients diagnosed with bladder cancer and agreed to be put in the study. The samples were stained with Immunohistochemistry Staining (IHC), and then we quantitatively counted the number of the Ki-67 stained nucleus on a microscope.

RESULTS: A total of 54 samples were obtained in this study. Samples consisted of 27 samples with NMIBC and 27 samples with MIBC. The cut-off point was 20%, we found 17 patients with MIBC and 14 patients with NMIBC presented with biomarker > 20%. Biomarker ≤ 20% was found in 10 patients with MIBC and 13 patients with NMIBC. On statistical analysis with Chi-Square test, no significant association found (p = 0.583) between KI-67 and muscle - invasiveness with OR of 1.579, 95% CI (0.533-4.678).

CONCLUSION: There is no association between expression of Ki-67 and muscle invasiveness in bladder cancer.

Introduction

Bladder cancer is a type of neoplasia in which the cell aligning the bladder lost its ability to control growth and cell division. Worldwide, bladder cancer ranked 9th commonly found neoplasia [1]. There are two known histopathological staging, **non-muscle invasive bladder cancer** (NMIBC), in which the mass was limited to mucous with no muscle involvement, and **muscle-invasive bladder cancer** (MIBC).

Majority of cases found was NMIBC [1][2]. Although this type of cancer can be managed easily by trans-urethral resection, the recurrence rate was 15%-75%, with 10% of cases progress into MIBC. MIBC tend to have a poor prognosis. It is imperative to develop an early diagnosis, as well as appropriate treatment in a patient with bladder cancer [3].

Immunohistochemistry is an established method that supports histopathologic assessment in the diagnosis of various benign and malignant diseases. In 1982, Nathrath et al. were the first to experiment on bladder cancer paraffin sample and documenting a set of keratin and carcinoembryonic antigen [3]. Since then, the prognostic value of immunohistochemistry marker becomes important. In the last two decades, immunohistochemistry evaluation, specifically regarding cell cycle and apoptosis, was intensively pursued to obtain a better understanding of prognosis in patient with bladder cancer. A prognostic biomarker is essential in which they can provide information on disease progression, regardless of intervention. Two types of prognostic biomarker were recognised, the biomarker which can give information of recurrence and biomarker which contain information of disease progression (progression-free survival). A predictive biomarker can provide information about the effect of an intervention, as well as able to be used as targeted

therapy [4]. Ki-67 is immunohistochemistry marker known to be present on an actively proliferating cell. Evidence has shown that Ki-67 is a predictive factor of cancer cell proliferation, expression of Ki-67 correlate with poor prognosis in several types of cancer [5][6]. Nevertheless, the value of

Ki-67 as the prognostic factor in bladder cancer remains controversial [7]; few studies result show that Ki-67 can predict progression and recurrence, while other studies show no significant correlation. One meta-analysis study by Tian et al. concludes that Ki-67 expressions correlate significantly with recurrence, progressivity, and lower survival only in Caucasian [8]. This research aims to evaluate the association between Ki – 67 expressions with MIBC and NMIBC.

Methods

This study was conducted at the Department of Pathology, University of Sumatera Utara, Indonesia. Samples were obtained from bladder cancer patient primary specimen paraffin blocks that were analysed in Pathology laboratory in 2013-2015. The patients have been confirmed agreed to be put in the study. Each group contained 27 samples. Samples were then stained with Immunohistochemistry Staining (IHC), and then quantitatively count the number of the Ki-67 stained nucleus on a microscope. The interpretation was made by calculating the amount of stained cell from 100 tumour cells, with cut-off point 20% as in Otto et al. study (≤ 20% counted as "low expression" and > 20% count as "overexpression") [9].

Results

Fifty-four samples, which consists of 27 samples with NMIBC and 27 samples with MIBC were obtained. Sample characteristics are shown in Table 1.

Table 1: Sample characteristics of NMIBC and MIBC

Variable	Group		p value
	NMIBC	MIBC	
	N = 27	N = 27	
Age	56.1 ± 11.43	60.5 ± 9.85	0.413*
Gender			
Male	25 (92.6%)	23 (85.2%)	0.669*
Female	2 (7.4%)	4 (14.8%)	
Grading			
High Grade	12 (44.4%)	27 (100%)	<0.001*
Low Grade	15 (55.6%)	0 (0%)	

*Chi-Square Test.

In NMIBC group, the mean age was 56.1 ± 11.43 years, while in MIBC was 60.5 ± 9.85 years. Male (twenty-three in MIBC and twenty-five in NMIBC) was more common than female (four in NMIBC and two in NMIBC) in both categories. In NMIBC group, more than half of samples were low grade (55.6%), and 44.4% high grade (p < 0.001). On the above table, sample characteristic on both groups from age and gender perspective didn't show a significant difference (p = 0.669).

Table 2: KI-67 Test Result on NMIBC and MIBC

Biomarker	Group		p-value	OR	95% CI
	NMIBC	MIBC			
	N = 27	N = 27			
KI 67 > 20	17 (63.0%)	14 (51.9%)			
			0.583*	1.579	(0.533-4.678)
< 20	10 (37.0%)	13 (48.1%)			

*Chi-Square Test.

We divided biomarker with the cut-off point of 20%, Ki-67 > 20% and Ki-67 ≤ 20%. For KI – 67 > 20%, we found 17 patients with MIBC and 14 patients with NMIBC. Biomarker ≤ 20% was found in 10 patients with MIBC and 13 patients with NMIBC. On statistical analysis with Chi-Square test, there was no significant association (p = 0.583) between KI-67 and muscle-invasiveness with OR of 1.579, 95% CI (0.533-4.678).

Discussion

Usage of the marker in tissue to help clinicians decision was successfully done in few malignancy cases. In a research conducted by Jonat and Arnold, evaluating Ki-67 and its function in clinical practice [10] significantly proves the importance of the utilisation of marker mentioned above to detect the proliferation of a tumour. Also shown in the research done by Heslin et al. [11], those in patients with soft tissue sarcoma, the increase in Ki-67 marker expressions proved as an independent prognostic tool to predict the metastasis and the mortality of a tumour. Several studies suggest the effectivity of Ki-67 as a prognostic marker.

Ki-67 is one of many biomarkers that can be detected by the monoclonal antibody as a proliferation marker. The usage of this immunohistochemistry is highly useful due to its rapid and accurate result to indicate the presence of ongoing proliferation rather than a solid tumour [12] In the recent years, studies about proliferation biomarkers are high in demand. Studies show that Ki-67 correlated significantly with tumour cells of bladder cancer, and is capable of calculating the prognostic factor of the disease [13].

The value of Ki-67 as a prognostic biomarker of urothelial malignancies in urinary tract system is depicted in the meta-analysis study conducted by Lei et al. [14]. Contraries to that, a survey was done by Acikalin et al. find that there is no statistically significant correlation between the expression of Ki-67 and tumour recurrence progressivity and mortality [8]. Instead, they detect the presence of Ki-67 correlate with tumour size and grading. The research above is congruent with the fact that our study did not find a statistically significant relationship between the presence of Ki-67 and bladder cancer progression. Several factors may have affected the result, such as incomplete biomarker data and a limited number of samples due to patient's reluctance to join our study.

This study concludes that there is no association between expression of Ki-67 and muscle invasiveness in bladder cancer. This result can be used as a reference for further research, as biomarker nowadays proved to be valuable in clinically to predict prognosis in the patient, as well as provide better intervention for the patient with prostate cancer.

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