RELATIONSHIP BETWEEN P53 EXPRESSION AND PROBABILITY OF ORGAN CONFINEMENT IN PATIENTS WITH PROSTATE CANCER IN SARDJITO HOSPITAL

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ABSTRACT

Objective: *To determine the association between p53 expression and the probability of organ confinement in patients with prostate cancer in Sardjito Hospital, Yogyakarta.* ***Material & method:*** *Prostate specimens were obtained from patients with clinical stage T1-T2 prostatic adenocarcinoma in Sardjito Hospital between January 2007 and December 2008. Samples were processed and immunohistochemically stained in the Department of Anatomical Pathology Gadjah Mada University. Probability of organ confinement was determined by updated Partin table 2007 from preoperative serum PSA level, Gleason Score, and clinical stage. Correlation between p53 expression and probability of organ confinement were statistically analyzed by Spearman correlation test.* ***Results:*** *There were 28 prostate cancer patients eligible for this study. Mean age was 65,19 ± 10,9 (28 - 81) years old. Mean preoperative PSA level were 107,13 ± 165,82 (0,20 734,20) ng/ml. Mean number of p53 expression was 97,47 ± 97,27 (5 - 396)/HPF. Significant correlation was found between p53 expression and probability of organ confinement (Spearman r = -0,441; p = 0,019).* ***Conclusion:*** *p53 expression was negatively correlated with the level of organ confinement in patients with prostate cancer.*

Keywords: *Prostate cancer, organ confinement, Partin table, p53, immunohistochemistry.*

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INTRODUCTION

Prostate cancer is a solid tumor most frequently found among males in the United States. Biological behavior of prostate cancer is varied and complicating the prediction of the course of the disease and prognosis of the patient. In the last two decades, incidence of prostate cancer worldwide is increasing along with increasing life expectancy and widespread prostate-specific antigen (PSA) screening. With the more popular use of PSA, more prostate cancer cases are found and there is a phenomenon of stage migration, in which the incidence of cancer in early stage is found more frequently than that in previous decade. Along with increased probability for surgical intervention, prediction of organ confinement becomes more important. Prognostic markers in use today, such as grading, clinical staging, and PSA level, still have limitation in predicting prognosis. Therefore molecular biomarkers to predict patients with organ-confined prostate cancer becomes necessary.[1]

Somatic mutation of tumor suppressor gene p53 has been reported as the basis of the pathogenesis of several neoplasms (breast, lung, colon, bladder, and prostate cancers), and has been proven as the most common genetic change occurring in carcinogenesis. Several studies have studied the role of p53 in prostate cancer. Even though some studies have indicated that gene p53 mutation does not commonly occur in early

stage prostate cancer, several current studies have shown that loss of p53 suppressor function may be an important step in disease progression. In addition, change of p53 expression in early stage cancer may be a prognostic marker. Furthermore, it is recognized that p53 mutations may underlie the process of hormone refractory prostate cancer.[2]

The p53 gene is a DNA gene of 20 kb in length, located on the short arm of chromosome 17 (17p13l). The p53 gene is comprised of 11 exons that code a 393-amino acid nuclear phosphoprotein (53 kDa). The loss of gene p53 allele on short arm of chromosome 17 at 17p13 often occurs in various types of tumor. The most frequent locations of gene mutation in several types of tumor are exons 5 to 8. Normal or wild (wt) type p53 protein has a very short half life, while the mutated (mt) type has longer half life. Therefore, mutant-type p53 can be more easily detected using immunohistochemical methods, and p53 immuno-reactivity is a reflection of gene p53 mutation.[3-5]

At present it is recognized that p53 functions as a tumor suppressor gene in inhibiting growth of tumor cells in vitro and in vivo. The p53 gene has an active role in the regulation of transition from G1 phase to S phase in cell cycle as a response to DNA damage. There is supporting evidence that p53 may inhibit expression of several genes enhancing the growth of cells (such as, c-fos and c-jun) by binding the proteins that regulate the cellular transcription process. Therefore, gene transcription regulation by p53 may play the primary role in negative regulation of cell growth.[5] Not only controlling cell cycle and DNA repair, the p53 gene also plays a role in apoptosis or programmed cell death, although its role in prostate cell apoptosis remains in debate.[6]

Previous studies have proved that there is significant correlation between p53 overexpression and tumor stage, which indicates that p53 gene mutation is the first event in the carcinogenesis of prostate cancer. Additionally, there is correlation between p53 overexpression with poor differentiation and high index of cell proliferation. Furthermore, increased p53 expression also correlates with the occurrence of metastasis as well as hormone resistance.[3-5]

OBJECTIVE

This study aims to identify correlation between p53 expression and the probability of organ confinement based on the Partin tables.

MATERIAL & METHOD

The subjects of this study were all prostate adenocarcinoma patients with clinical stage T1 - 2, diagnosed between January 1, 2007 and December 31, 2008, in Sardjito Hospital, Yogyakarta. The inclusion criteria were (1) prostate adenocarcinoma patients established with histopathological examination, (2) the clinical stage of the patients were T1c, T2 (a - c) and has been confirmed by urologists (AJCC-TNM, 2002), (3) pre-operative serum PSA level was examined, and (4) the degree of tumor differentiation was known (Gleason Score). The exclusion criterion was unknown probability of organ confinement due to incomplete examination. In this study, Partin tables published in 2007 was used to predict the probability of organ confinement of each patient, which was determined from a combination of serum PSA level, Gleason Score, and clinical stage.[1]

Serum PSA level was measured pre-operatively in the Clinical Pathology Laboratory, Sardjito Hospital. The degree of differentiation was determined according to the Gleason system based on anatomic pathology examination to prostate specimens obtained from needle biopsy. Clinical stage used in this study was the T stage, determined with digital rectal examination, based on AJCC-TNM year 2002. P53 staining procedure was performed at Anatomic Pathology Laboratory, Sardjito Hospital, using anti p53 D-O7 monoclonal antibody. p53 expression was examined by a single pathologist by counting p53-containing nuclei in each preparation. The examination of each preparation was performed in five visual fields, and result was determined from those five visual fields. Correlation between p53 expression and the probability of organ confinement was analyzed statistically using bivariate analysis. Prior to analysis, data normality test was performed using one-sample Kolmogorov-Smirnov technique. When the data was normally distributed, bivariate

analysis was performed with Pearson's correlation test. In contrast, when the data were not normally distributed, Spearman's correlation test was employed. Data were analyzed by means of statistical analysis program, SPSS version 15.0.

RESULTS

During the study period, there were a total of 28 males with mean age of 65,19 ± 10,9 (28 - 81) years who met the criteria and enrolled as subjects of study. The characteristics of the patients can be seen in table 1. The mean of pre-operative serum PSA level was 107,13 ± 165,82 (0,20 - 734,20) ng/ml and the mean of total p53 expression was 97,47 ± 97,27 (5 - 396)/high power field.

Table 1. Subject characteristics.

Patients (n)	28
Age (years), mean ± SD (interval)	65,19 ± 10,9 (28 - 81)
PSA serum level (ng/ml)	
0 2,5	2 (7,14%)
2,6 4,0	1 (3,57%)
4,1 6,0	0 (0%)
6,1 8,0	0 (0%)
8,1 10,0	0 (0%)
> 10,0	25 (89,29%)
Clinical stage (AJCC-TNM 2002)	
T1a	0 (0%)
T1b	0 (0%)
T1c	3 (11,53%)
T2a	4 (15,38%)
T2b	5 (19,23%)
T2c	14 (53,84)
Gleason sum	
2 - 4	5 (17,86%)
5 - 6	5 (17,86%)
3 + 4	3 (10,71%)
4 + 3	1 (3,57%)
8 -10	14 (50%)

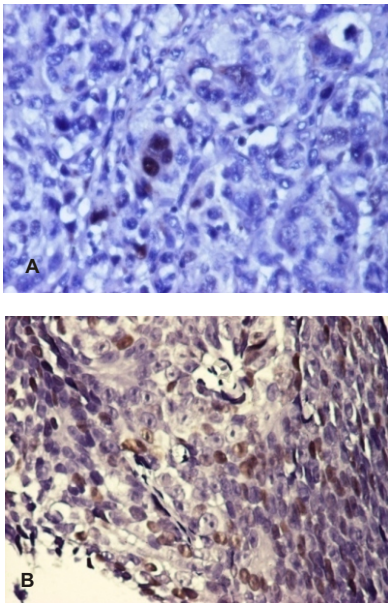

Figure 1. P53 expression in patients with prostate adenocarcinoma, marked with brown-stained nuclei. (A) p53 expression in patients with high probability of organ confinement (T2c, t-PSA = 1,41 ng/ml, Gleason Score = 2 + 3; probability of organ confinement = 84%). (B) p53 expression in patients with low probability of organ confinement (T2c, t-PSA = 50 ng/ml, Gleason Score = 4 + 4; probability of organ confinement = 12%).

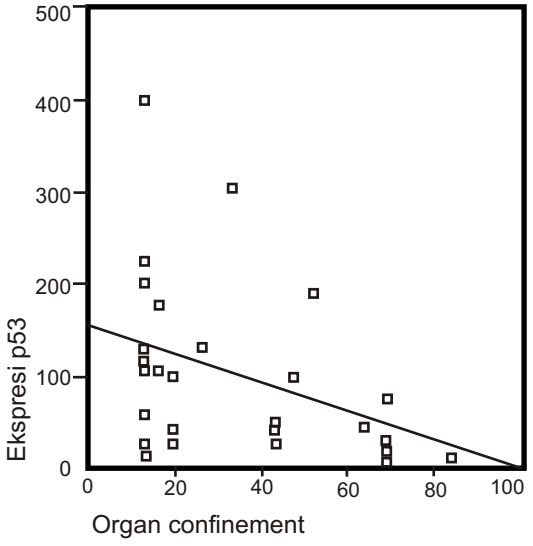

Figure 2. Correlation between p53 expression and organ confinement.

Tabel 2. Correlation between p53 expression and organ confinement.

			Organ Confinement	Expression p53
Spearman's rho	Organ Confinement	Correlation Coefficient	1,000	-,441(*)
		Sig. (2-tailed)	.	,019
		N	28	28
	P53 expression	Correlation Coefficient	-,441(*)	1,000
		Sig. (2-tailed)	,019	.
		N	28	28

DISCUSSION

Mutation of tumor suppressor gene p53 is a genetic change underlying much of carcinogenesis in several types of tumor. A number of studies have shown that p53 immunoreactivity is correlated with a high histological grade, DNA aneuploidy, and a high rate of cell proliferation. Therefore it is also suggested to have correlation with prostate cancer aggressiveness. In addition, p53 gene mutation is expected to correlate with high recurrent risk and hormone refractory prostate cancer.

In this study we combined the factors of clinical stage, serum t-PSA level and Gleason Score in assessing probability of organ confinement (based on Partin Tables) and its correlation with p53 expression was examined. The result of this study revealed statistically significant negative correlation between p53 expression and organ confinement probability in patients with T1-2 prostate adenocarcinoma patients ($p < 0,05$). This indicates that with higher p53 expression, probability of organ confinement in prostate cancer patients is lower. Higher p53 expression means higher p53 gene mutation, from wild type (wt) p53 with a short half life to a mutated type (mt) p53 with longer half life. Results of this study confirms that of Downing et al (2001) who concluded that gene p53 mutation is related with prostate cancer progressiveness.[7] The results also confirmed the study by Papadopoulos et al (1996) and da Slavov et al (2006), who suggested correlation between high p53 expression and more advanced tumor stage and pathological status.[8] A study by Miyake et al (2008) also concluded that the increase of p53 expression is also a predictor in determining surgical margin status (SMS), lymph node metastasis and tumor volume.[9]

CONCLUSION

P53 expression in the nuclei of prostate adenocarcinoma patients may serve as a marker of organ confinement probability. Patients with high p53 immunoreactivity have low probability of organ confinement. Therefore, assessment of p53 expression can be used as additional clinical parameter used in assessing prostate cancer progressiveness, in addition to serum PSA level, Gleason Score, and examination of tumor margins by digital rectal examination.

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