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The Role of Androgen Receptor Expression in Prostate Adenocarcinoma

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Abstract

BACKGROUND: Androgen receptor (AR) plays a role in the growth and differentiation of male urogenital structures, both under normal and neoplastic conditions, the neoplastic condition is caused by the mechanism of the AR pathway which undergoes changes that continue in the development and progression of prostate lesions, both benign and malignant. AR s are generally found evenly distributed in the nuclei of glandular and stromal cells in prostate hyperplasia and vary widely in prostate cancer.

AIM: This study is conducted to learn more about the role of AR expression in adenocarcinoma prostate grading.

METHODS: An observational analytical study with cross-sectional methods was carried out among 77 respondents who were selected using consecutive sampling. Prostate adenocarcinoma was taken from resection tissue of prostate cancer patients using TRUS biopsy which was interpreted as adenocarcinoma prostate with a grading using Modified Gleason Grading System (WHO/International Society of Urological Pathology 2016) or referred as the WHO Grade Group I, II, III, IV, and V in hematoxylin eosin staining. AR expression was calculated using the Histological score (H-score) formula. The research was conducted at the anatomical pathology laboratory of Hasanuddin University Hospital Makassar from August to October 2020.

RESULTS: There was a statistically significant difference between AR expression score and histopathological feature of prostate adenocarcinoma WHO Grade Group ($p < 0.001$).

CONCLUSION: Based on our findings, there is a significant correlation between AR and WHO Grade Group and we highly recommended in further study of prostate adenocarcinoma that these variables could be used as biomarker in prostate adenocarcinoma grading progression.

Introduction

Prostate cancer is the most common type of cancer worldwide after lung, breast, and colorectal cancer. Based on data from Globocan, International Agency for Research on Cancer 2018, all cancer cases in men, 1.3 million cases (7.1%) were prostate cancer cases with 359,000 deaths (3.8%), puts prostate cancer as the most common type of cancer in men after lung cancer [1], [2]. The incidence of prostate cancer has increased significantly above 60 years old. The highest percentage occurred in the 60–70 year age group, which was 64%. The degree of prostate malignancy is currently using a new scoring system that is simpler and more accurate to provide a histopathological feature of prostate malignancy. This system has been recommended by the World Health Organization (WHO) in 2016, that the degree of prostate malignancy uses grading group. Based on the International Society of Urological Pathology Consensus, the grading group used the Gleason scoring system and the latest modification in 2014 [3].

Androgen receptor (AR) is a phosphoprotein to mediates the action of testosterone and 5-α-dihydrotestosterone (DHT) through mechanism of AR as a transcription factor, which is AR plays a role in the growth and differentiation of male urogenital structures, under either normal or neoplastic condition. AR inhibitor is used to treat prostate adenocarcinoma by inhibiting androgen synthesis. The quantity of prostate cancer cells which are androgen-sensitive can be seen through the immunohistochemical expression of AR. The assessment of AR expression can be used in determining therapy and predicting the success of hormonal therapy so that the prognosis of the disease will be better [4]. Sensitization of androgenic responses by multifunctional growth factor signaling pathways is one of the mechanisms, where AR causes androgen-independent prostate cancer. Androgen-induced proliferation of prostate epithelial cells is regulated by an indirect pathway involving paracrine mediators produced by stromal cells, such as insulin-like growth factor (IGF) [5].

Androgen ablation therapy has been the main therapy for prostate cancer for many years.

This therapy initially shows a good response, but the frequent recurrence of tumors makes this therapy less effective. Metastatic of prostate cancer most commonly involves bone and initially is androgen dependent. There is a progression to androgen independent after androgen therapy within 12–18 months. Thus, an approach is needed to identify other parameters, namely, the interaction of AR and IGF-IR as a target for prostate cancer therapy [6]. This study using immunohistochemical staining to detect AR expression in prostate cancer was the first to be conducted using samples received in Anatomical Pathology Laboratory, Faculty of Medicine, Hasanuddin University. By knowing AR expression in prostate adenocarcinoma based on the WHO Group grading system, we hope that this study can contribute to determining the prognosis and therapeutic targets of prostate malignancy.

Research Methods

This study is an analytical observational study with cross-sectional methods to determine AR expression in prostate adenocarcinoma grading. With a cross-sectional design, it is hoped that this study will serve as a follow-up evaluation of the role of AR expression in prostate adenocarcinoma which is relatively inexpensive and efficient. This research was conducted at the anatomical pathology laboratory of Hasanuddin University Hospital Makassar from August to October 2020. The research sample was selected using consecutive sampling methods that fulfill inclusion and exclusion criteria. Inclusion criteria in this study included tumor tissue that had been sent and assessed by a pathologist as prostate adenocarcinoma according to the WHO Grade Group with hematoxylin eosin staining. Exclusion criteria included damaged prostate tumor tissue preparations, paraffin block preparations from damaged tumor tissue, and incomplete patient identity sheets. The estimated sample using Lemeshow's formula is minimal around 46 samples based on the incidence of prostate adenocarcinoma in Indonesia and we found 77 samples as the final sample. The research population was taken from resection tissue of prostate using TRUS biopsy that was sent to the anatomical pathology RSUP Dr. Wahidin, Unhas Hospital, and Makassar Pathology Diagnostic Center from January to June 2020, which was diagnosed as prostate adenocarcinoma with a grading determined by the Modified Gleason Grading System (WHO/ International Society of Urological Pathology 2016) or referred as the WHO Grade Group I, II, III, IV, and V in hematoxylin eosin staining. Samples that met the inclusion criteria were re-evaluated by two Pathologists and then proceeded with immunohistochemical staining to observe the expression of AR in the sample by combining two parameters, which are the intensity and percentage of stained area. The percentage of stained area and the intensity was assessed on the cell nucleus for AR which was calculated using the Histological score (H-score) formula. Histological score as the percentage of the immunopositive nuclei (0–100%) multiplied by a value corresponding to level of intensity (0 none/uncolored, 1 weak positive, 2 moderate positive, and 3 strong positive) and the result ranged between 0 (no staining in the tumor) and 300 (diffuse strong staining of the tumor). Positive AR expression intensity based on apocrine differentiation in the tumor cells. The apocrine differentiation was identified based on cytologic features such as abundant granular eosinophilic cytoplasm, cytoplasmic vacuolization/ clearing, round vesicular nuclei, and with prominent eosinophilic oftenly or basophilic nucleoli. If any of the cytoplasmic and nuclear features were present in >10% of the tumor cells, the tumor was considered as apocrine differentiation [7]. The collected data samples were grouped based on purpose and the data were not normally distributed. The statistical method used univariate analysis to described general characteristics and bivariate analysis using the Kruskal–Wallis test to compare between AR expression score and WHO Grade Group. Samples were continued with the Mann–Whitney Test to assess the mean difference between 2 test groups in the WHO Grade Group based on AR expression H-score.

Results

Sample characteristic

This research was conducted from August to October 2020 with a total sample of 77 respondents. The age distribution of the sample is about 93.5% of the total patients at the age of ≥50 years old (Table 1), the distribution of histopathological features based on the WHO Grade Group in this sample was equally distributed. In the sample of the WHO Grade Group I, there were at least 14 cases (18.2%), while the number of the WHO Grade Groups III, IV, and V were 20 cases (20.8%) in each grade.

Table 1: Analysis of the relationship between two groups of the WHO GRADE GROUP adenocarcinoma prostate based on AR expression H-Scores using Mann–Whitney test

Mann–Whitney test	WHO Grade Group				
	I	II	III	IV	V
I	0.000	0.093	0.064	0.043*	0.006*
II		0.000	0.264	0.572	0.001*
III			0.000	0.780	0.004*
IV				0.000	0.017*
V					0.000

*Significant P < 0.05, except same groups pair.

Based on Table 2, the highest expression of AR that was found strongly expressed was 40 samples (51.9%), followed by moderate expression by 33 samples (42.9%), weak expressed AR was found

on three samples (3.9%), and unstained/negative expression of AR samples are one sample (1.3%). A comparison of prostate adenocarcinoma tissue is shown in Figure 1. AR expression was stained with brown in the nucleus of the cells determined by the intensity and the area. Based on AR expression, the weak positive (a) well-defined nodule with minimal infiltration, the shape, and size of the gland began to vary, describing the gland as larger, shaped, and oval. Moderate positive (b) describes glands that were more infiltrative, more varied in size and shape, generally small, angular in shape, irregular in shape, varying in distance between glands. Strong positive (c) describes poorly recognizable glands, poorly formed lumen, fused, or cribriform gland pattern (including glomeruloid pattern) and hypernefromatoid.

Table 2: Sample characteristic based on age, histopathological features based on WHO Grade Group, score, and expression of AR (n = 77)

Characteristic	n	%
Age		
< 50	5	6,5
≥50	72	93,5
WHO grade groups		
I	14	18,2
II	15	19,5
III	16	20,8
IV	16	20,8
V	16	20,8
AR expression		
Unstained/Negative	1	1,3
Weak positive	3	3,9
Moderate positive	33	42,9
Strong positive	40	51,9

Relationship between AR expression H-score with histopathological features in prostate adenocarcinoma based on the WHO Grade Group

Based on the analysis of the relationship between AR expression scores and histopathological features, the mean expression scores of prostate adenocarcinoma were almost the same in each WHO Grade Group, respectively, 2.70 ± 0.49; 3.06 ± 0.58; 2.99 ± 0.65; and 3.20 ± 0.52, except WHO Group Grade I with 1.54 ± 1.06 (Table 3).

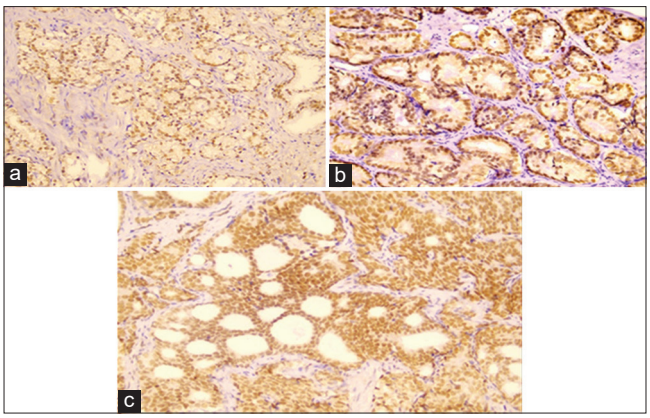

Figure 1: Positive AR expression in prostate adenocarcinoma (a) Weak Positive, (b) Moderate Positive, and (c) Strong Positive. (Objective 20×)

The results of the Kruskal–Wallis test p < 0.001 show that there is a significant relationship between the AR expression H-Score with histopathological features of adenocarcinoma based on the WHO Grade Group.

Table 3: Analysis of the relationship between AR expression H-scores and histopathological features of prostate adenocarcinoma based on the WHO grade group with Kruskal–Wallis test

Kruskal-Wallis test	AR expression H-score	
	Mean ± SD	Min-Max
I	1.54 ± 1.06	0.01–3.20
II	2.70 ± 0.49	1.80–3.60
III	3.06 ± 0.58	1.80–3.60
IV	2.99 ± 0.65	1.50–3.60
V	3.20 ± 0.52	2.40–3.60

Kruskal–Wallis test P < 0.001 (p < 0.05).

The relationship of AR expression between two prostate adenocarcinoma WHO Grade Groups

Based on Kruskal–Wallis test, there was a significant relationship between AR expression H-score and histopathological grading of prostate adenocarcinoma based on the WHO Grade Group, it is necessary to conduct further analysis of the relationship between each of the WHO Grade Group. The analysis was done by comparing nominal variables between two unpaired groups using the Mann–Whitney test.

The results of the comparative analysis of AR expression H-score between groups of prostate adenocarcinoma WHO Grade Groups were three WHO Grade Group pairs except the same groups pair were significantly different, between I versus IV; I versus V; II versus V; III versus V; and IV versus V with p value, respectively, 0.043; 0.006; 0.001; 0.004; and 0.0017 (Table 1). However, there were some pairs of the WHO Grade Groups that showed insignificant differences in AR H-Score, which are I versus II; I versus III; II versus III; II versus IV; and III versus IV.

Discussion

Based on the results of this study, it was shown that there was a significant difference between the AR Expression Score and the five Histopathological Features of the WHO adenocarcinoma Grade Group using the Kruskal–Wallis test (Table 3). The mean expression score of prostate adenocarcinoma was almost the same between WHO Groups grades II, III, IV, and V and there was a tendency where the higher a grade, the higher the H-score obtained, especially in the WHO GRADE GROUPs III–V.

ARs are generally found to be evenly distributed in the nuclei of glandular and stromal cells in prostate hyperplasia, but vary widely in prostate cancer. The quantity of androgen-sensitive prostate cancer cells can be seen through the immunohistochemical

expression of AR. The neoplasm condition is caused by the mechanism of the AR pathway which undergoes changes that continue in the development and progression of prostate lesions, both benign and malignant. In normal prostate gland cells, transcription and apoptosis occur in a balanced state. Meanwhile, in prostate cancer cells, there is an imbalance between transcription and apoptosis which result in excessive growth, and then malignancy occurs. In prostate cancer, the rate of proliferation is higher than cell death, where androgens and AR are the main regulators of the proliferation-death ratio of these cells. Therefore, AR expression increased in line with the aggressiveness of prostate adenocarcinoma growth associated with its grading.

AR gene mutation is thought to be one of the pathogenesis pathways of prostate malignancy. According to Velcheti *et al*., in the normal prostate, activation of AR initiated by DHT occurs autocrinely in the stromal cell nucleus and paracrinely by diffusion to nearby epithelial cell nuclei. In the paracrine pathway, AR in the nucleus of stromal cells plays an important role in promoting stromal cells to produce growth factors (adromedine) which bind to basal cells. Basal cells as progenitors bind to androedins and undergo proliferation and differentiation into luminal cells. In the paracrine phase, AR in the epithelial cell nucleus (luminal cells/acinar cells) functions to maintain homeostasis of luminal cells and suppress proliferation of basal cells [8].

Molecular changes due to AR mutations cause changes in the AR axis which results in changes in which the autocrine pathway stands alone without being followed by a paracrine pathway mechanism, thereby triggering the activation of the growth of cancer cells to survive and proliferate. The autocrine process in adenocarcinoma causes AR to stimulate the proliferation of malignant epithelial cells and maintain them to become cell-autonomous cells. Cell-autonomous develops independently of stromal cells as in the paracrine pathway. Pathologically, AR signaling in cell-autonomous cells allows androgen or androgen complexes to bind to abnormal genes that are regulated in intermediate cells or malignant luminal cells to survive and proliferate [9].

A recent analysis of clinical prostate cancer specimens also collected from patients without pre-operative treatment which showed that high AR expression correlates with lower recurrence-free survival and disease progression [10]. The results of this study are similar to the results of research by Hashmi *et al*., who, in 2019, also found that patients with low-grade WHO group did not show strong AR expression, on the other hand, patients with high-grade WHO group showed strong AR expression [11]. Furthermore, we found another research that has been done in our country by Putriyuni and Oktora found a significant correlation between AR expression and WHO Grade Group, where prostate adenocarcinoma samples with high Gleason scores expressed AR 5× more strongly than samples with low Gleason scores [12]. It is concluded that there is a significant difference between the AR Expression Score and the five histopathological features of the WHO adenocarcinoma Grade Group. This research has several limitations such as only examined AR expression in adenocarcinoma prostate pathogenesis, so it did not have comparative data for each pathway. Other confounding factors of the sample were not investigated. The limitation of the study is the small sample size, the study was done on historical archival samples of patients with prostate cancer, samples of control group were not available, the authors recommend for an extension of this study to include control group and correlate the data of expression of ARs to data on genetic markers of PCa. We hope; further, study may discover the AR as targeted therapies of prostate adenocarcinoma.

Conclusion

There is a significant relationship between AR and WHO Grade Group, which is concluded as higher AR expression score then WHO Grade Group is higher. According to these results, we highly recommend in further study AR expression that could be used as biomarker in grading prostate adenocarcinoma progression with large samples size and control group.

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