RESEARCH ARTICLE

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Prognostic Significance of High Androgen Receptor Expression in Prostatic Acinar Adenocarcinoma

Atif Ali Hashmi[1]*,Ghazala Mudassir[2],Muhammad Irfan[3], Zubaida Fida Hussain[1], Shumaila Kanwal Hashmi[4], Huda Asif[5], Laila Nisar[6], Maheen Naeem[6], Naveen Faridi[1]

Abstract

Background: Quantitative immunohistochemical expression of Androgen receptor (AR) has not been evaluated as a prognostic biomarker of prostate cancer in our population, therefore in the current study we aimed to evaluate the association of AR expression in prostatic acinar adenocarcinoma with various prognostic parameters like tumor quantification, Gleason score, WHO grade group and perineural invasion. **Methods:** Total 121 cases of biopsy proven prostatic acinar adenocarcinoma were selected from records of pathology department archives from January 2013 till December 2017. Hematoxylin and eosin stained slides and paraffin blocks were retrieved and new sections were cut where necessary. Slides of all cases were reviewed by two senior histopathologists and pathologic characteristics like Gleason score, WHO grade, tumor quantification, perineural and lymphovascular invasion were evaluated. Androgen receptor immunohistochemistry was applied on all cases. **Results:** Low AR expression was noted in 53 cases (43.8%) while high AR expression was seen in 68 cases (56.2%). Significant association of AR expression was noted with total Gleason score, WHO grade and percentage of tissue involvement (tumor quantification). Univariate binary logistic regression showed patients with low Gleason scores (scores 6,7 or 8) and low WHO grade (grade 1, 2 or 3) were less likely to express high AR expression in comparison to high Gleason score (score 9) and high WHO grade group (grade 5) respectively. Similarly, cases with low tissue involvement by carcinoma (<50%) were less likely to show high AR expression in comparison to cases with >50% tissue involvement by carcinoma. **Conclusion:** Significant association of AR expression was noted with total Gleason score, WHO grade and percentage of tissue involvement (tumor quantification) which are among the most important markers of tumor progression; therefore we suggest that AR expression should be performed in patients with prostatic adenocarcinoma for prognostic stratification of the patients.

Keywords: Androgen receptor- AR- prostatic carcinoma- Gleason score- WHO grade group

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Introduction

Androgens (testosterone and dihydrotestosterone) act through androgen receptor (AR) and this interaction is required for normal prostate development (Roy et al., 1999; Cunha et al., 1987). It is believed that prostatic carcinogenesis is androgen mediated, however serum androgens can't promote carcinogenesis alone, hence functional status of androgen receptor (AR) is the most important mediator of prostate cancer progression. Low serum testosterone in prostate cancer patients was found to be associated with high AR expression which in turn is linked to higher Gleason score (Schatzl et al., 2002). Recent studies also revealed that high AR expression was correlated with disease progression and lower recurrence free survival (Lee, 2003). Quantitative immunohistochemical (IHC) expression of AR has not been evaluated as a prognostic biomarker of prostate cancer in our population, therefore in the current study we aimed to evaluate the association of AR expression with various prognostic parameters like tumor quantification, gleason score, WHO grade group and perineural invasion.

Materials and Methods

Case Selection: Total 121 cases of biopsy proven prostatic acinar adenocarcinoma were selected from records of pathology department archives. All patients underwent surgeries at Liaquat National hospital, Karachi from January 2013 till December 2017 over a period of 5 years. The study was approved by research and ethical review committee of Liaquat National Hospital and

*[1]Department of Histopathology, [3]Department of Statistics, Liaquat National Hospital and Medical College, [6]Liaquat National School of Diagnostic Laboratory Sciences, Karachi, [2]Department of Pathology, Shifa College of Medicine, Islamabad, [4]Department of Pathology, CMH Institute of Medical Sciences, [5]CMH Institute of Medical Sciences, Multan, Pakistan. *For Correspondence: doc_atif2005@yahoo.com*

informed written consent was taken from all patients at the time of surgery. Hematoxylin and eosin stained slides and paraffin blocks were retrieved and new sections were cut where necessary. Slides of all cases were reviewed by two senior histopathologists and pathologic characteristics like Gleason score, WHO grade, tumor quantification, perineural and lymphovascular invasion were evaluated. Specimens included prostatic chips and radical prostatectomies. Moreover, representative tissue blocks of all 121 cases were selected for AR immunohistochemistry (IHC).

Androgen Receptor (AR) Immunohistochemistry: AR IHC was performed using DAKO EnVision method using monoclonal mouse anti-human androgen receptor; clone AR441 according to manufacturer's protocol (dilution of 1:50). Nuclear staining for AR was both quantitatively and qualitatively evaluated. Intensity of staining was scored into no staining (0), weak (1+), intermediate (2+), strong (3+) while percentage of positively stained cells were scored as continuous variable (figure 1). Intensity and percentage scores were multiplied to generate an H-score ranging from 0-300. A cut-off value of 200 was used to categorize AR expression into low and high.

Statistical Analysis: Statistical package for social sciences (SPSS 21) was used for analysis. Mean and standard deviation were calculated for quantitative variables. Frequency and percentage were evaluated for qualitative variables. Normality was checked by Shapiro wilk test. Mean comparison was done by using mann whitney U test and Kruskal wallis H test as appropriate. Chi square test was applied to determine association. Odds were calculated for significant variables by univariate binary logistic regression. P-value ≤0.05 was taken as significant.

Results

Patients Characteristics: Mean age of the patients was 67.81+10.12 years. 22.3% (27 cases) and 30.6% (37 cases) were of Gleason score 8 and 9 respectively. There was no case of Gleason score 10 or below 6. Similarly, 30.6% (37 cases) were having WHO grade group 5. 52.1% (63 cases) revealed >50% tissue involvement by prostatic carcinoma. Perineural invasion was noted in 37.2% (45 cases) as shown in Table 1.

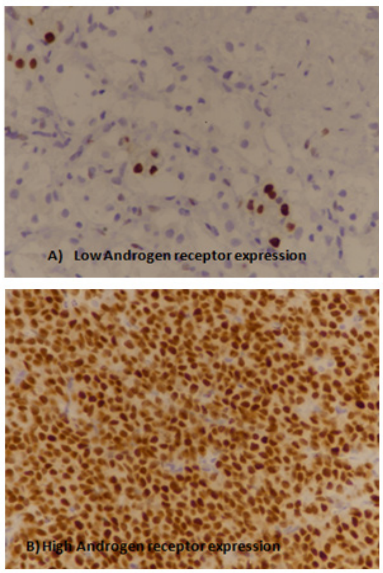

Figure 1. Androgen Receptor (AR) Expression in Prostatic Acinar Adenocarcinoma, A) Low AR expression, 100X magnification, B) High AR expression, 100X magnification

Androgen receptor expression: Low AR expression was noted in 53 cases (43.8%) while high AR expression was seen in 68 cases (56.2%). Significant association

Table 1. Clinicopathologic Characteristics of Studied Population (n=121)

	n (%)
Age (years)	
Mean±SD	67.81±10.12
Groups	
<40 years	2 (1.7)
40-70 years	75 (62)
>70 years	44 (36.4)
Tumor Quantification (%)	
Mean±SD	47.59±32.16
Groups	
<10 %	29 (24)
10-50 %	29 (24)
>50 %	63 (52.1)
Total gleason score	
6	22 (18.2)
7	35 (28.9)
8	27 (22.3)
9	37 (30.6)
WHO grade group	
Grade 1	22 (18.2)
Grade 2	17 (14)
Grade 3	18 (14.9)
Grade 4	27 (22.3)
Grade 5	37 (30.6)
Perineural invasion	
Present	45 (37.2)
Absent	76 (62.8)
Lymphovascular invasion	
Present	3 (2.5)
Absent	118 (97.5)
Extraprostatic extension	
Present	8 (6.6)
Absent	113 (93.4)
Seminal vesicle invasion	
Present	6 (5)
Absent	115 (95)
Androgen Score	
Mean±SD	71.52±21.84
Groups	
Low Expression	53 (43.8)
High Expression	68 (56.2)

Table 2. Association Androgen Receptor Expression with Clinicopathologic Parameters in Prostatic Acinar Adenocarcinoma

	n (%)		P-Value
	Low Expression (n=53)	High Expression (n=68)	
Age Group↕			
<40 years	0 (0)	2 (2.9)	0.536
40-70 years	32 (60.4)	43 (63.2)	
>70 years	21 (39.6)	23 (33.8)	
Total gleason score			
6	18 (34)	4 (5.9)	0
7	22 (41.5)	13 (19.1)	
8	7 (13.2)	20 (29.4)	
9	6 (11.3)	31 (45.6)	
WHO grade group			
Grade 1	18 (34)	4 (5.9)	0
Grade 2	12 (22.6)	5 (7.4)	
Grade 3	10 (18.9)	8 (11.8)	
Grade 4	7 (13.2)	20 (29.4)	
Grade 5	6 (11.3)	31 (45.6)	
Tumor Quantification			
<10	21 (39.6)	8 (11.8)	0
10-50	17 (32.1)	12 (17.6)	
>50	15 (28.3)	48 (70.6)	
Perineural invasion			
Present	22 (41.5)	23 (33.8)	0.385
Absent	31 (58.5)	45 (66.2)	
Lymphovascular invasion↕			
Present	2 (3.8)	1 (1.5)	0.581
Absent	51 (96.2)	67 (98.5)	
Extraprostatic extension↕			
Present	6 (11.3)	2 (2.9)	0.136
Absent	47 (88.7)	66 (97.1)	
Seminal vesicle invasion↕			
Present	5 (9.4)	1 (1.5)	0.085
Absent	48 (90.6)	67 (98.5)	

Chi square test applied; ↕Fisher exact test applied; P-Value≤0.05; considered as significant.

of AR expression was noted with total Gleason score, WHO grade and percentage of tissue involvement (tumor quantification). Statistically insignificant association of AR expression was noted with other variables including perineural invasion, lymphovascular invasion, extra-prostatic extension and seminal vesicle invasion (Table 2). Perineural invasion was noted in 33.8% of tumors showing high AR expression. Similarly, lymphovascular invasion, extra-prostatic extension and seminal vesicle invasion was seen in 1.5%, 2.9% and 1.5% of cases respectively, however, the association with AR expression was not significant (p=>0.05).

Univariate binary logistic regression showed that patients with low Gleason scores (scores 6,7 or 8) and low

Table 3. Odds Ratio for Patients with High Androgen Expression

	odds ratio (95% CI)	P-Value
Total gleason score		
6	0.043 (0.011-0.173)	0
7	0.114 (0.038-0.347)	0
8	0.553 (0.162-1.886)	0.344
9®	1	
WHO grade group		
Grade-I	0.043 (0.011-0.173)	0
Grade-II	0.081 (0.021-0.315)	0
Grade-III	0.155 (0.043-0.555)	0.004
Grade-IV	0.553 (0.162-1.886)	0.344
Grade-V®	1	
Tumor Quantification		
<10	0.119 (0.044-0.323)	0
10-50	0.221 (0.086-0.564)	0.002
>50®	1	

Univariate binary logistic regression was applied; P-Value≤0.05, considered as significant.

Table 4. Comparison of Mean Androgen Receptor Expression (H-Score) with Clinicopathologic Parameters

	Mean±SD	P-Value
Age Group™		
<40 years	90.00±0.000	0.188
40-70 years	70.26±24.18	
>70 years	72.84±17.43	
Total gleason score™		
6	57.27±26.75	0
7	62.85±23.14	
8	75.37±14.73	
9	85.40±10.16	
WHO grade™		
Grade 1	57.27±26.75	0
Grade 2	66.47±18.68	
Grade 3	59.44±26.78	
Grade 4	75.37±14.73	
Grade 5	85.40±10.16	
Tumor Quantification™		
<10	65.17±18.77	0.001
10-50	62.58±29.89	
>50	78.57±15.92	
Perineural invasion		
Present	71.33±21.56	0.644
Absent	71.64±22.14	
Lymphovascular invasion		
Present	76.66±2.88	0.652
Absent	71.39±22.10	
Extraprostatic extension		
Present	55.62±32.34	0.054
Absent	72.65±20.64	
Seminal vasicle invasion[a]		
Present	74.16±3.76	0.237
Absent	71.39±22.38	

Mann-Whitney U test was applied.™Kruskal-Wallis H test was applied. P-Value≤0.05, considered as significant.

WHO grade (grade 1, 2 or 3) were less likely to express high AR expression in comparison to high Gleason score (score 9) and high WHO grade group (grade 5) respectively. Similarly, cases with low tissue involvement by carcinoma (<50%) were less likely to show high AR expression in comparison to cases with >50% tissue involvement by carcinoma as shown in table 3.

Table 4 shows comparison of mean H-score of AR expression with various clinicopathologic parameters revealing significant association of mean high AR expression with higher tumor grade and high tissue involvement by carcinoma.

Discussion

In the present study we evaluated AR expression in prostatic acinar adenocarcinoma and found high AR expression in 56.2 % of cases. Moreover, high AR expression was associated with high tissue involvement by tumor and higher tumor grade and Gleason score which are among the most important markers of disease progression in prostatic tumors. To our knowledge, this is among the first study in Pakistan evaluating the prognostic significance of AR expression in prostatic carcinoma.

AR acts an important biomarker in many human cancers especially of genital tract (Hashmi et al., 2018). Prognostic significance of high AR expression has been studied previously. Some authors observed that high AR expression correlates with better tumor differentiation (i.e low Gleason score) (Chodak et al., 1992; Lee et al., 2003; Takeda et al., 1996) while other researchers found a contradictory observation (Hobisch et al., 1996; de Winter et al., 1994). Loss of AR expression in some tumor cells (low AR expression) can be due to many reasons like X-chromosome losses (Alers et al., 2000; Nupponen et al., 1998) or epigenic gene silencing (Sasaki et al., 2002). We found low AR expression in 44% of cases.

Major limitation of our study was limited number of cases and lack of patients follow up. However, we found that high AR expression is associated with higher percentage of tissue involvement by tumor and higher tumor grade which has important clinical significance.

Significant association of AR expression was noted with total Gleason score, WHO grade and percentage of tissue involvement (tumor quantification) which are among the most important markers of tumor progression; therefore we suggest that AR expression showed be performed in patients with prostatic adenocarcinoma for prognostic stratification of the patients.

Statement conflict of Interest

All authors declare that there is no conflict of interest.

References

Alers JC, Rochat J, Krijtenburg PJ, et al (2000). Identification of genetic markers for prostatic cancer progression. *Lab Invest*, **80**, 931.

Cunha GR, Donjacour AA, Cooke PS, et al (1987). The endocrinology and developmental biology of the prostate. *Endocr Rev*, **8**, 338-62.

Chodak GW, Kranc DM, Puy LA, et al (1992). Nuclear localization of androgen receptor in heterogeneous samples of normal, hyperplastic and neoplastic human prostate. *J Urol*, **147**, 798-803.

De Winter JR, Janssen PJ, Sleddens HM, et al (1994). Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. *Am J Pathol*, **144**, 735.

Hashmi AA, Hussain ZF, Qadri A, et al (2018). Androgen receptor expression in endometrial carcinoma and its correlation with clinicopathologic features. *BMC Res Notes*, **11**, 289.

Hobisch A, Culig Z, Radmayr C, et al (1996). A. Androgen receptor status of lymph node metastases from prostate cancer. *Prostate*, **28**, 129-35.

Lee D, Oh W, Sartor O (2003). High androgen receptor levels are predictive of decreased survival in prostate cancer. *Clin Prostate Cancer*, **2**, 13-4.

Lee DK, Chang C (2003). Expression and degradation of androgen receptor: mechanism and clinical implication. *J Clin Endocrinol Metabol*, **88**, 4043-54.

Nupponen NN, Kakkola L, Koivisto P, Visakorpi T (1998). Genetic alterations in hormone-refractory recurrent prostate carcinomas. *Am J pathol*, **153**, 141-8.

Roy AK, Lavrovsky Y, Song CS, et al (1998). Regulation of androgen action. *Vitam Horm*, **55**, 309-352.

Sasaki M, Tanaka Y, Perinchery G, et al (2002). Methylation and inactivation of estrogen, progesterone, and androgen receptors in prostate cancer. *J Nat Cancer Inst*, **94**, 384-90.

Schatzl G, Madersbacher S, Gsur A, et al (2002).Association of polymorphisms within androgen receptor, 5α-reductase, and PSA genes with prostate volume, clinical parameters, and endocrine status in elderly men. *Prostate*, **52**, 130-8.

Takeda H, Akakura K, Masai M, et al (1996). Androgen receptor content of prostate carcinoma cells estimated by immunohistochemistry is related to prognosis of patients with stage D2 prostate carcinoma. Cancer: Interdisciplinary. *Int J Am Cancer Soc*, **77**, 934-40.