International Journal of Medical Science and Clinical Invention 7(11): 5125-5129 2020
DOI:10.18535/ijmsci/v7i11.10 **ICV: 77.2**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article,

Androgen Receptor Expression of Prostate Cancer Correlates with Gleason Score and Perineural Invasion in West Sumatera, Indonesia

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Abstract:
Prostate cancer is the second most common and the fifth leading cause of death by cancer in men worldwide now. The failure of androgen deprivation therapy (ADT) for prostate cancer caused by activated androgen receptor (AR) signaling pathways mostly found. The role of AR in growth and progression of prostate cancer is still unclear. Analysis of AR expression in prostate cancer has never been done in West Sumatera. This study aims to determine AR expression of prostate cancer and correlate with Gleason score and perineural invasion. A total of 56 prostate cancer from department of anatomical pathology in West Sumatera. Hematoxylin and eosin (HE) stained slides and paraffin blocks were retrieved. Slides of all cases were evaluated to review Gleason score, histopathological grading, WHO grade group based on ISUP 2014/WHO 2016 and perineural invasion. Androgen receptor immunohistochemistry (IHC) was applied on all cases. High AR expression was the mostly found (51, 79%). The mostly prostate cancer is Gleason score 9 (44,64%), histopathological grading poorly differentiated/undifferentiated (76,78%), WHO grade group 5 (48,21%). Perineural invasion was noted in 39, 29%. There was significant statistical correlation between AR expression and Gleason score, but no significant correlation with perineural invasion. AR expression is the important marker of prostate cancer progression.

Key words: AR expression, prostate cancer, West Sumatera Barat, Indonesia

Introduction:

Prostate cancer connotes adenocarcinoma prostate is the malignant neoplasm.[1] It is curently the second most common cancer in the worldwide after lung cancer in males based on GLOBOCAN IARC 2018. It is reported 1,3 million (7,1%) new cases, increasing from 2012 (1,1 million). Prostate cancer is the fifth leading cause of death by cancer in males.[2,3] Cancer Registry of Indonesian Pathologist Association in 2014 reported that prostate cancer is the fourth most common from 10 males primary tumour in Indonesia. The cases in Padang city 2014 is reported 80 cases that the second most common from 10 males primary tumour, increasing from last years.[4]

The growth, progression and metastase of prostate cancer are highly influenced by AR signaling, that is critical singnaling for prostate cancer. Androgen receptor plays important roles in initiation and progression of prostate cancer, but its mechanism is still unclear. Androgen deprivation therapy is the principal therapy for prostate cancer with local and metastase. Over time the most cancer cells show AR signaling pathways activated during ADT which causes resistance.[5,6]

The diagnose of prostate cancer is using a system by Gleason score that is applied by pathologist since a long time ago. This system was introduced for the first time by Donald F. Gleason, which is used widely for prostate cancer. The score results from Gleason system is the strong predictor for biological behavior of prostate cancer cells and one

of significant prognostic factor to asses' prostate cancer progression and metastase.[7] another prognostic factor is perineural invasion that is one of the main mechanisms for cancer cell extraprostatic dissemination (38-93%). Perineural invasion is marked by cancer cells infiltration in, around and through the nerves microscopically.[8] there is no study on correlation between AR expression and prognostic parameters of prostate cancer such as Gleason score and perineural invasion, particularly West Sumatera, Indonesia.

Procedures and methods:

Total 56 cases of prostate cancer were selected from records of anatomical pathology department archieves in West Sumatera. The study was approved by local research and ethical review committee. Hematoxylin and eosin (HE) stained slides and paraffin blocks were retrieved. Slides of all cases were evaluated to review Gleason score, histopathological grading, WHO grade group based on ISUP 2014/WHO 2016 and perineural invasion (*Figure 1*). Gleason score was grouped into low grade (Gleason score < 8) and high grade (Gleason score 8-10). Specimens included prostatic chips and prostatectomies. Moreover, representative tissue blocks of all 56 cases were selected for IHC examination. IHC staining has been carried out at Anatomical Pathology Department of RSUP Dr. Cipto Mangunkusumo, Jakarta. We used primary antibody monoclonal AR441 (DAKO, dilution of 1:100). Positive controls were benign lesion of prostate. Nuclear staining for AR was semi-quantitatively evaluated. Percentage of positive cell (PP) was scored into 0,1,2,3,4 (0, 1= <10%, 2= 10-50%, 3=51-80%, 4= >80%) and staining intensity (SI) was scored 0,1,2,3 (0=negative, 1=weak, 2= intermediate, 3= strong) (*Figure 2*). Percentage and intensity scores were multiplied to generate immunoreactive score (IRS) ranging from 0 – 12. The interpretation was 0-1= negative, 2-3= mild, 4-8= moderate, 9-12= strong. A cut-off value of 9 was used to categorized AR expression into low and high. Statistical analysis for quantitative variables were mean and standard deviation. Frequency and percentage were evaluate for qualitative variables. Chi-square test was applied to determine correlation. Odds were calculated for significant variables by Mantel-Haenzel Common Odds Ratio (OR). P-value < 0, 05 was taken as significant.

Results:

Mean age of patients was 70,68±7,99 years. The most prostate cancer cases were Gleason score 9 (44,64%), histopathological grading poorly differentiated/ undifferentiated (76,78%), grade group 5 (48,21%). Perineural invasion was noted in 39,29%. Low AR expression was noted in 48,21% (27 cases) while high AR expression was seen in 51,79% (29 cases) as shown in *Table 1*. Significant correlation of AR expression was noted with Gleason score (p=0,018) and OR=5,098 (CI=1,233-21,254). It indicated that prostate cancer with high grade Gleason score had 5,098 time's high AR expression rather than low AR expression (*Table 2*). Statistically insignificant correlation of AR expression was noted with perineural invasion (*Table 3*).

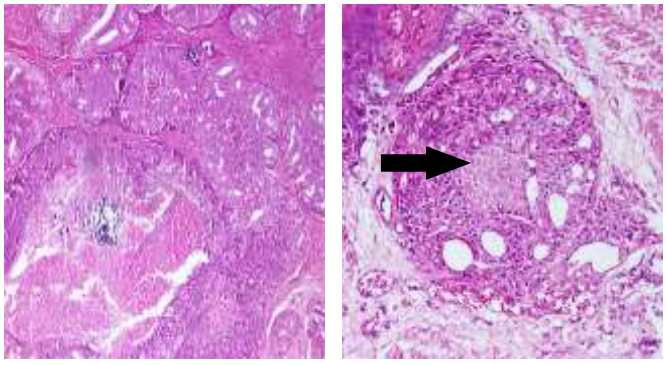

Figure 1. Histopathology of prostate cancer. A. Gleason score 9 (HE 200x), B. Perineural invasion (black arrow) (HE, 200x)

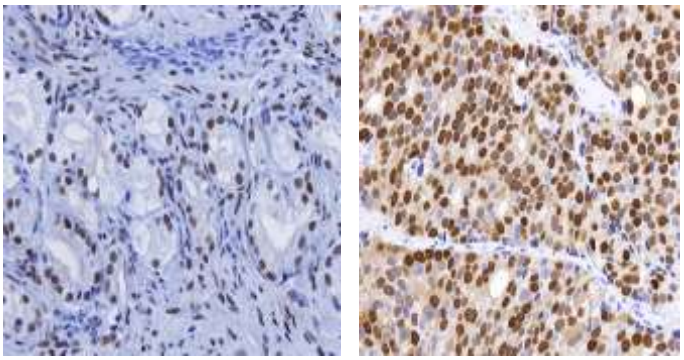

Figure 2. AR expression of prostate cancer, A. Low AR expression (400x), B. High AR expression (400x)

Table 1. The Subject Characteristic of Study

Characteristic	f (n = 56)	%
Age (years)		
Mean±SD	70,68±7,	
Gleason Score (GS)	99	
6		1,79
7	1	21,43
8	12	28,57
9	16	44,64
10	25	3,57
Histopathological Grading	2	
Well Diff (GS ≤6)		1,79
Moderately Diff (GS 7)	1	21,43
Poorly Diff/Undiff (GS 8-10)	12 43	76,78
WHO *Grade Group*		
Grade 1		1,79
Grade 2	1	14,29
Grade 3	8	7,14
Grade 4	4	28,57
Grade 5	16	48,21
Invasi Perineural	27	
Absent		60,71
Present	34	39,29
Ekspresi Protein AR	22	
Low		48,21
High	27 29	51,79

Table 2. Correlation between AR Expression with Gleason score of Prostate Cancer

AR Expression	Gleason score		Total f (%)	P-Value	OR (CI)
	Low Grade f (%)	*High Grade* f (%)			
Low	10 (37,0)	17 (63,0)	27 (100)	0,018	5,098 (1,233-21,254)
High	3 (10,3)	26 (89,7)	52 (100)		
Total	13 (23,2)	43 (76,8)	56 (100)		

Table 3. Correlation between AR Expression with Perineural Invasion of Prostate Cancer

AR Expression	Perineural Invasion		Total f (%)	P-Value
	Absent f (%)	Present f (%)		
Low	16 (59,3)	11 (40,7)	27 (100)	0,830
High	18 (62,1)	11 (37,9)	29 (100)	
Total	34 (60,7)	22 (39,3)	56 (100)	

Discussion:

Androgen receptor, the biomarker which is important in many human cancer especially genital tracts, including prostate cancer. One of the study stated that the most positively AR expression (95%) reported in prostate cancer rather than others urogenital cancer, with sensitivity 94,8%, specificity 81,4% and 73% strongly positive.[9] Our study found high expression AR in 51,80% of prostate cancer cases. This result similar with Hashmi et al. that reported the most prostate cancer with high AR expression in 56,2% (68 cases).[10] As well as Lekshmy and Prema reported AR expression in the almost all prostate cancer cases.[11] AR signaling pathway is very important in initiation and progression of prostate cancer. High AR expression is significantly prognostic factor for prostate cancer in many studies. A few studies reported high AR expression as the result of gene amplification. It caused lost of growth control with activated tumor cells more sensitive to androgen castration level of prostat. Besides, high AR expression can also increase response to ADT so that increasing survival rate.[10,12] The higher proliferation and progression of tumor cells, the worse differentiation grading based on histopathology. High proliferation and progression indicate poorly biological behavior, have effect to histopathologic as the worse prognostic at the end. The study found high grade Gleason score (Gleason score 8-10) had more high expression AR rather than low expression AR. There is significant correlation AR expression with Gleason score and OR=5,098 (CI=1,233-21,254). It means that prostate cancer with high grade Gleason score showed 5,098 time's high AR expression rather than low AR expression. Hashmi et al. also found significant correlation high AR expression in tumor cells and high grade Gleason score. Gleason score dan grade group are the crucial marker in determining progression of prostate cancer. This shows that high AR expression correlates with progression of prostate cancer.[10] The study by Chen et al. reported significant correlation high AR expression with bone metastase of prostate cancer cases rather than without metastase (p<0,001).[13] Therefore, AR expression examination can be used as prognostic predictor for prostate cancer.[10] But, some studies reported different results as Park et al.[12] and Husain et al.[14] which found statistically insignificant correlation with Gleason score. High AR expression correlates with well differentiated

of tumor cells (low grade Gleason score). Loss or low AR expression in some tumor cells may be caused by several things as lost of X-chromosome or epigenetic gene silencing.[10] This variation of results may also be caused by heterogeneous AR expression in prostate cancer cells, difference in antibodies used to detect AR receptor, and difference in counting positively tumor cells.[11] The study found low AR expression in 48,21% cases.

Perineural invasion is the interaction of tumor cells with surrounding nerves, induces a signal that support cancer progression.[15] The clinical importance of perineural invasion in cancer is still unclear. In our study shows that high AR expression has no significant correlation with perineural invasion. Overall, the high percentage of AR expression was found in absence of perineural invasion. Similar findings were reported by Hashmi et al., Lekshmy and Prema.[11,12] The role of nerves in growth and metastase of cancer was first discovered in prostate cancer. Several studies are currently showing stimulation effect from tumor nerves and neurosignaling in prostate cancer. The predominant mechanism of neurosignaling is adrenergic and cholinergic signaling. Prostate cancer cells can induce the growth of nerves (axonogenesis) via secretion of neurotrophic growth factor. Neurosignaling pathways promote the growth and metastase of prostate cancer.[16]

Conclusion:

The most prostate cancer cases in West Sumatera were high AR expression and high grade Gleason score. Significant correlation of AR expression was noted with Gleason score. Both of them are the crucial marker of prostate cancer progression. Examination of AR expression can determine the prognostic of prostate cancer.

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