Androgen Receptor as a Prognostic Marker in Adenocarcinoma Prostate

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ABSTRACT

Background & Objective: Prostate cancer is the second most common malignant tumor found in males. Androgen Receptor plays an important role in the development of normal as well as malignant prostatic tissue. The objective of this study was to see frequency of Androgen receptor in different grades of Gleason's scoring system of Prostatic carcinoma.

Methodology: It was descriptive cross sectional study conducted in department of pathology, King Edward Medical University and Urology Department of Mayo Hospital, Lahore from 1st Jan, 2015 to 31st Dec, 2015. Data was collected using purposivenon probability sampling technique from 60 cases of prostatic cancer diagnosed on histopathology. Histopathological Grading evaluation was performed using the Gleason scoring system. Data entry and analysis was done by using SPSS version 22.

Results: The mean age out of a total number of 60 cases was 67.33 ± 8.806 year with minimum and maximum age of 45 and 85 years. According to histological grades, 7 (11.67%) cases had low grade, 5 (8.33%) cases had intermediate and 48 (80%) cases had high grade tumor. In this study Androgen receptor was detected in 59 (98.33%) and it was not detected in 1 (1.67%) of the cases. As in 1 (1.67%) case Androgen was not detected so its score was 0, in cases whom androgen was detected there were 5 (8.33%) had +1 score, 25 (41.67%) cases had +2 score and 29 (48.33%) had score as +3.

Conclusion: AR is a diagnostically useful marker for prostate adenocarcinoma. Tumors with high grades have shown strong positive expression for AR. Also, Gleason score and AR expression have shown direct relationship with each other.

Key words: Androgen receptor, prostate adenocarcinoma, Histopathology.

INTRODUCTION

Prostate carcinoma is the second leading cause of deaths due to malignancies in American males.[1] Prostatic carcinoma has the highest incidence in America, Canada, Australia, and France as compared to Asian countries. However, the mortality rate is greater in low risk countries than other high-risk countries. By 2030, it is estimated that the universal load of new cases of prostate carcinoma would be increased upto 1.7 million along with 499,000 deaths due to massive increase in global population.[2] Prostate carcinoma has an incidence of 3.8% in Pakistan being the fourth most common malignancy of men.[3] This is due to deficiency in screening practices and lower life expectancy.[4]

Prostate cancer has an unclear etiology despite of high morbidity and mortality. Race, increasing age along with positive family history; are its established risk factors. High androgen levels, fatty meals, red meat consumption, minimum exercise and obesity are also other risk factors being reported, but their role in development of disease is controversial.[5]

Most of the prostatic carcinoma patients do not present any symptoms during its initial stages. However, they complain of lower urinary tract symptoms at later stages.Bone pain arising in pelvis or back may also be observed in some patients having an advanced or metastatic disease. Such patients must undergo digital rectal examination (DRE) and serum prostate specific antigen (PSA) levels. Biopsy is performed only in case of raised serum PSA level and an abnormal DRE finding.[6,7] At present, a PSA level of 4 ng/ml is taken as the cut off value for performing prostate biopsy.[8]

Gleason scoring is a system widely used for grading adenocarcinoma prostate, which classifies it into five grades depending on the glandular patterns of differentiation, having 1 as the least aggressive and 5 as the most aggressive. Gleason score is determined by adding the two numbers together. Staging in prostate cancer depends upon PSA value, DRE findings, prostate biopsy results, along with Gleason score. The pathological staging depends on size of the tumor, number of involved lymph nodes, and metastatic disease. Selection of treatment modality for prostate cancer is dependent on staging.[7] The current treatment includes prostatectomy and radiation therapy augmented with

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hormonal treatment.[9] Prostatic cancer recurs commonly and majority of the patients develop metastatic deposits. New targeted therapies for aggressive forms of prostate carcinoma are needed.[10]

"Androgen receptor (AR)" is a 110 KD nuclear receptor located on Xq11-12. It mediates transcription of target genes upon activation of androgens thus modifying growth and differentiation of prostate epithelial cells. Androgens and androgen receptor signaling are important for enlargement and preservation of prostate gland.[11]

SUBJECTS AND METHODS

Sample Collection and Processing

This descriptive study included 60 formalin fixed, processed and paraffin embedded tissue blocks of prostate adenocarcinoma collected from the Department of Pathology, King Edward Medical University/Mayo Hospital, Lahore after the approval of synopsis by Ethical Board/Institutional Review Board (IRB) and Advanced Study & Research Board (AS&RB). These formalin-fixed, paraffin-embedded tissue blocks were cut by microtome; the slides were prepared and stained with hematoxylin and eosin. Nuclei of cells were stained as blue and cytoplasm as pink. The prepared H & E stained slides were analyzed by two histopathologists to confirm the diagnosis of prostate adenocarcinoma. Histopathological grading evaluation was performed using Gleason grading and scoring system.

Gleason's Grading & Scoring System for Carcinoma Prostate on H & E staining Gleason Grade[12]

This is based on various architectural patterns of prostate adenocarcinoma that are graded from 1 to 5 as follows:

Gleason Score[13,14]

Prostate cancers comprise of more than one morphological/architectural patterns, the commonest or primary pattern and less common or secondary pattern. Both primary and secondary patterns are individually graded from 1-5 as described above. These grades or patterns are then finally summed up to obtain a combined Gleason grade/Gleason score ranging from 2-10. Based upon Gleason score, they are further classified into following three groups:

Table 1: *Gleason grading system for prostate adenocarcinoma.*

Gleason Grade	*Morphology*
Grade-1	Uniform, round closely packed glands forming well circumscribed nodules
Grade-2	Round, less uniform loosely packed glands
Grade-3	Single, small, infiltrating glands with wide stromal separation
Grade-4	Cribriform, fused, small acinar poorly formed glands
Grade-5	Sheets, cords, single cells or comedo carcinoma

Histological Grade	*Low Grade (well-Differentiated)*	*Intermediate Grade*	*High Grade*
Gleason score	≤ 6	7	8-10

Immunohistochemistry

Formalin fixed, paraffin wax embedded tissue blocks of histopathologically diagnosed cases with representative areas of tumor were then stained by immunohistochemistry for AR.

Evaluation of AR Expression on Immunohistochemistry Staining

For **Androgen Receptor** status, **nuclear** labeling in more than 10% neoplastic cells was considered as the cut-off point for positivity.[15] Positive controls included prostatebenign hyperplasia for AR and sections incubited without primary antibodies served as negative controls.

In order to assess the intensity of AR immunostaining from 0-3+ a visual scoring technique was devised, for each of 100 randomly selected nuclei.[16]

Where 0 = No staining;
1+ = Weak staining;
2+ = Moderate staining &
3+ = Strong staining.

Heterogeneous, faint granular nuclear staining was considered as **weak staining** while homogeneous, granular dark brown nuclear staining was considered as **strong staining.** Any staining which was more than weak staining and less than strong staining was considered as **moderate staining.**[17]

Statistical Analysis

Data entry and analysis was done by using SPSS version 22 (Statistical Package for Social Sciences). Quantitative variables were presented as mean ± SD. Qualitative variables were presented as frequency tables and percentages. The relationships between the different parameters were determined by Pearson chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period from January 2015 to December 2015; a total of 60 cases of prostate adenocarcinoma on which anti-androgen receptor (SP107) Rabbit monoclonal antibody immunohistochemistry was

performed after confirming the diagnosis of prostate cancer. The mean age of cases was 67.33 ± 8.806 year with minimum and maximum age of 45 and 85 years (Table 2).

Out of a total of 60 biopsies, 57 (95%) were TURP, 1 (1.67%) was a TRUS guided biopsy, 1 (1.67%) was a core needle biopsy and 1 (1.67%) was a radical prostatectomy specimen (Table 3).

The mean Gleason score was 8.22 ± 1.075 with minimum and maximum Gleason score as 6 and 10 (Table 4).

The hematoxylin and eosin stained slides of all sixty cases were evaluated for Gleason scoring and grading of prostate adenocarcinoma. Gleason score of ≤ 6 is low grade, 7 is intermediate grade and 8 to 10 is high grade prostate adenocarcinoma. According to these histological grades, 7 (11.67%) cases had low grade or well differentiated tumor, 5 (8.33%) cases had intermediate grade tumor and 48 (80%) cases had high grade tumor (Figure 1).

Table 2: *Descriptive statistics of patient's age (years) (n = 60).*

	Minimum	*Maximum*	*Mean*	*Std. Deviation*
Age (Years)	45	85	67.33	± 8.806

Table 3: *Percentages of Types of Prostatic Biopsies Received (n = 60).*

	TURP	*TRUS Guided*	*Core Needle Biopsy*	*Suprapubic Prostatectomy*
No. of Cases (%) 60	57 (95%)	1 (1.67%)	1 (1.67%)	1 (1.67%)

Table 4: *Descriptive Statistics of Gleason score (n = 60 cases).*

	Minimum	*Maximum*	*Mean*	*Std. Deviation*
Gleason Score	6	10	8.22	±1.075

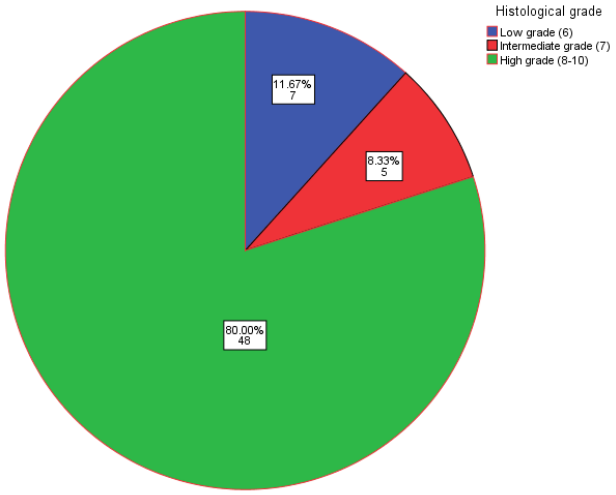

Fig. 1: *Percentage of Histological grades of Prostatic Carcinoma Based on Gleason Scoring.*

There were 7 (11.67%) patients who had a Gleason score of 6, 5 (8.33%) cases had Gleason score of 7, 19 (31.67%) cases had Gleason score of 8, 26 (43.33%) cases had Gleason score of 9 and 3 (5%) cases had Gleason score of 10 (Figure 2).

The Androgen receptor staining score was identified as 3+, 2+ and 1+ in three cases, two cases and two cases respectively among the seven cases that were labeled as Gleason score of 6. Two out of five cases labeled with Gleason score of 7 showed AR staining score of 3+ while the remaining three of them showed

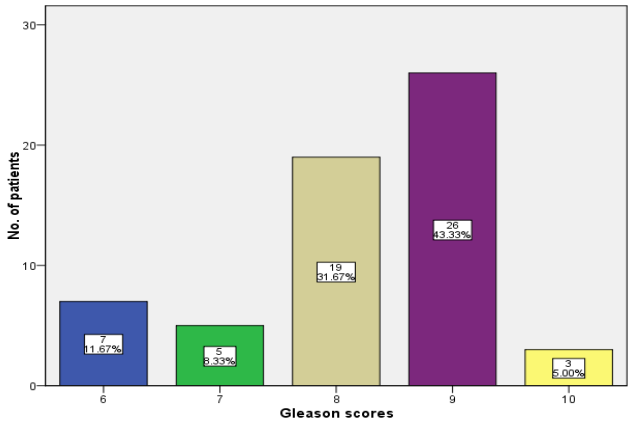

Fig. 2: *Figure showing number of cases with Percentages of Gleason scores in Prostatic cancers.*

AR staining score of 1+. No case had a score of zero or 2+. There were nineteen cases labeled with Gleason score of 8. Eleven of them showed AR intensity score of 2+ and eight cases showed AR intensity score of 3+. Twenty six cases were diagnosed as Gleason score of 9, of which fourteen cases showed AR intensity score of 3+, eleven cases were identified with AR intensity score of 2+ and only one of them was labeled as AR intensity score of 1+. There were only three cases with Gleason score 10 of which two cases showed AR intensity score AR of 3+. Only one case with Gleason score of 10 showed zero intensity for Androgen Receptor activity. This single case of AR negativity having Gleason score of 10 was histologically classified as sarcomatoid variant of Prostate Adenocarcinoma. The *p*-value was 0.000 which showed the strong association (Table 5).

Seven out of sixty cases were of low grade (Gleason score 6) of which 2 cases, 2 cases and 3 cases showed weak = 1+, mode-rate = 2+ and strong staining inten-

sity = 3+ respectively. Five out of sixty cases represented intermediate grades (Gleason score 7) of which 3 cases showed weak = 1+, 2 cases showed strong staining intensity = 3+ while none of the case showed moderate staining intensity = 2+. Both low and intermediate grades have not shown any case of negative or zero AR score. Forty eight cases out of a total of sixty cases were high grade (Gleason score 8-10), of which only one case was labeled as AR negative or zero staining. These high grade cases showed staining scores as 0, 1+, 2+ and 3+ in 1case, 1 case, 22 cases, and 24 cases respectively. The *p*-value was 0.002 which shows that histologically high grade prostate adenocarcinomas (Gleason score of 8-10), significantly expressed Androgen receptor (AR) as compared to intermediate (Gleason score of 7) and low grade (Gleason score of 6) tumors (Table 6).

In this study Androgen receptor positivity was detected in 59(98.33%) cases and not detected in only 1 (1.67%) case (Figure 3).

The intensity of Androgen receptor antibody staining in tumor cells was also evaluated according to previous literature and categorized into scores as:

No staining = 0
Weak staining = 1+
Moderate staining = 2+
Strong staining = 3+

nuclear staining was considered as **strong staining.** Any staining which was more than weak staining and less than strong staining was considered as **moderate staining**.

Table 5: *Association of Gleason score with Androgen Receptor Inten-sity score.*

Gleason Scores	*Androgen Receptors Score*				*Total*
	0 Score	*1+*	*2+*	*3+*	
6	0	2	2	3	7
7	0	3	0	2	5
8	0	0	11	8	19
9	0	1	11	14	26
10	1	0	0	2	3
Total	1	6	24	29	60

p-value by Pearson Chi-square test = 0.000, Only one case having Gleason score of 10 which is histologically classified as sarcomatoid variant of prostatic adenocarcinoma was found to be significant because it showed zero Androgen Receptor score.

Table 6: *Association of Histological Grade and Androgen Receptor Intensity Score.*

Histological Grade	*Androgen Receptors Score*				*Total*
	0 Score	*+1*	*+2*	*+3*	
Low grade (Gleason score 6)	0	2	2	3	7
Intermediate (Gleason score 7)	0	3	0	2	5
High grade (Gleason score 8-10)	1	1	22	24	48
Total	1	6	24	29	60

p- value by using Pearson Chi-Square test = 0.002
High grade (Gleason score 8-10) prostatic carcinomas were significantly found to express Androgen Receptor.

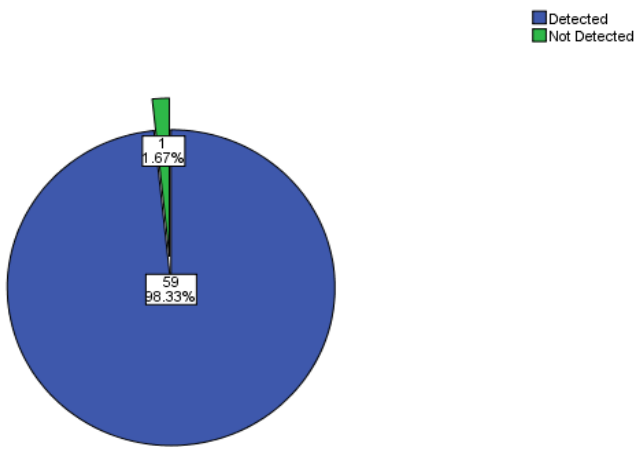

Fig. 3: *Distribution of Androgen Receptor status as evaluated on microscopy.*

In cases where Androgen receptor was detected, 6 cases (10%) had 1+ score, 24 cases (40%) had 2+ score and 29 cases (48.33%) had score of 3+. As in 1 (1.67%) case Androgen was not detected so its score was 0.Out of total 60 cases 6 cases (10%) showed weak staining, 24 cases (40%) showed moderate staining and 29 cases (48.33%) showed strong Androgen Receptor immunostaining. Only one case showed no staining at all (Figure 4).

Heterogeneous, faint granular nuclear staining was considered as **weak staining** while homogeneous, granular dark brown

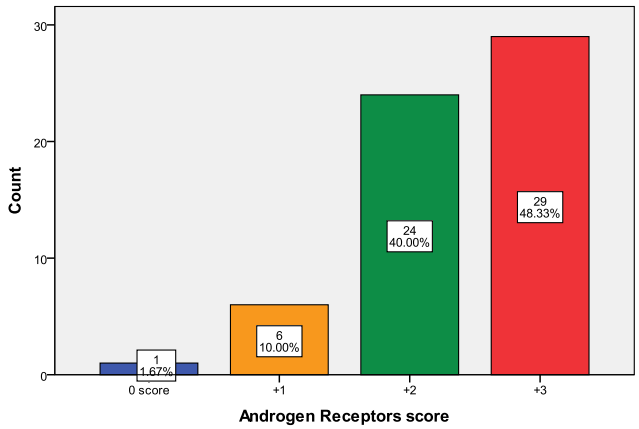

Fig. 4: *Figure showing Distribution of Androgen Receptor score as evaluated on microscopic examination according to following criteria.*

No staining	= 0	Moderate staining	= 2+
Weak staining	= 1+	Strong staining	= 3+

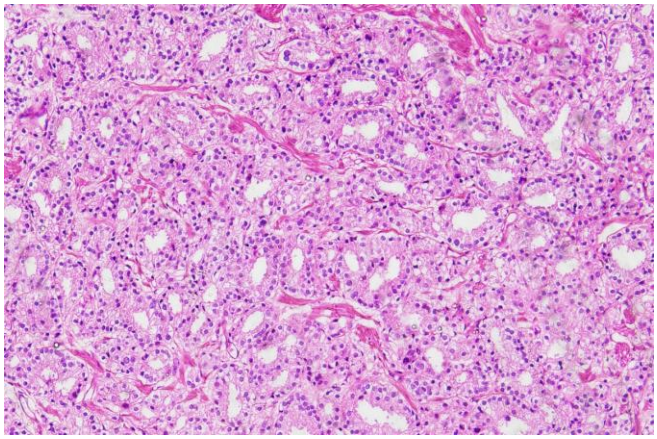

Fig. 5: *Prostate adenocarcinoma with Gleason score 7 (H & E stain, 100x magnification).*

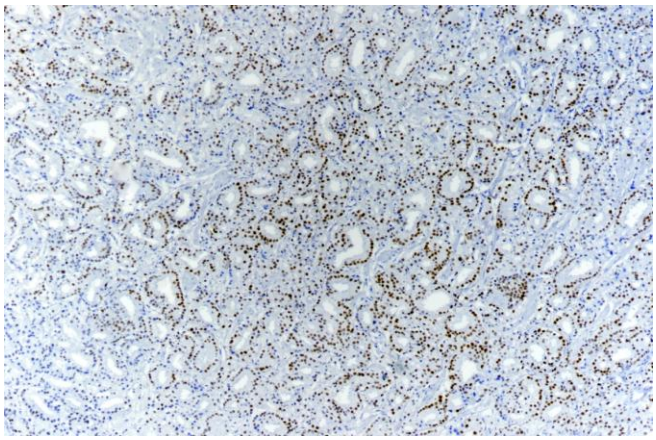

Fig. 6: *Same case of Prostate Adenocarcinoma with Gleason Score 7 showing AR staining score 1+ (IHC stain, 100x magnification).*

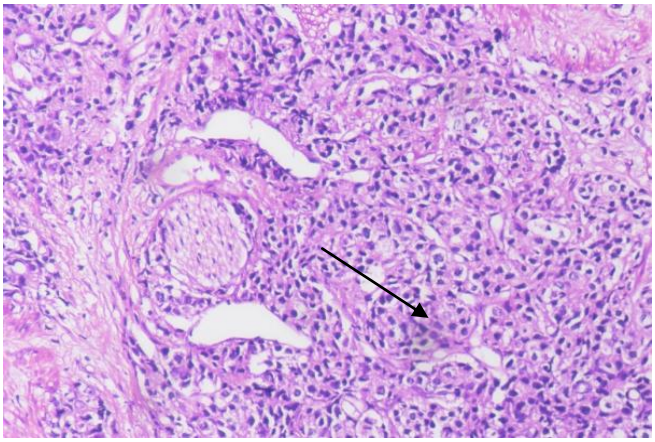

Fig. 7: *Prostate Adenocarcinoma with Gleason Score 9 showing Perineural invasion (Arrow) (H & E stain, 200X magnification).*

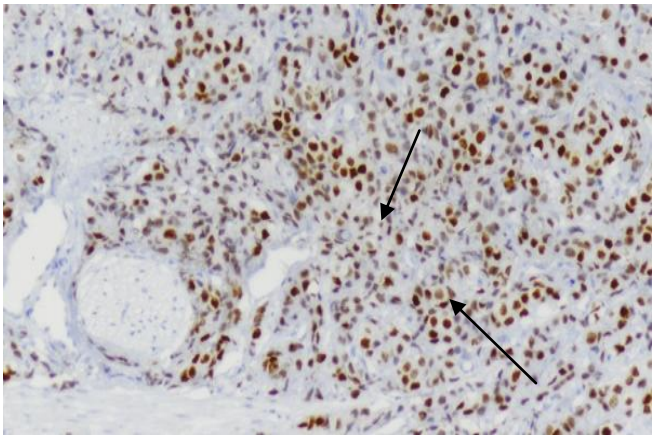

Fig. 8: *Same case of Adenocarcinoma Prostate with Perineural invasion (Arrow) showing AR staining score 2+ (IHC stain, 200X magnification).*

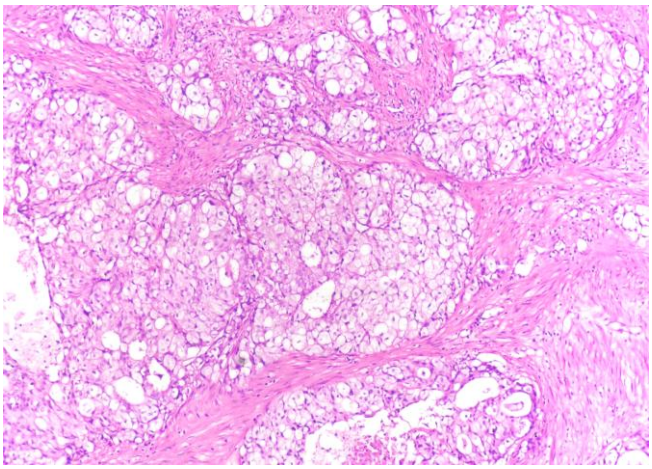

Fig. 9: *Prostatic Adenocarcinoma showing both Hypernephroid & Comedo pattern with Gleason Score 9 (H & E stain, 100X magnification).*

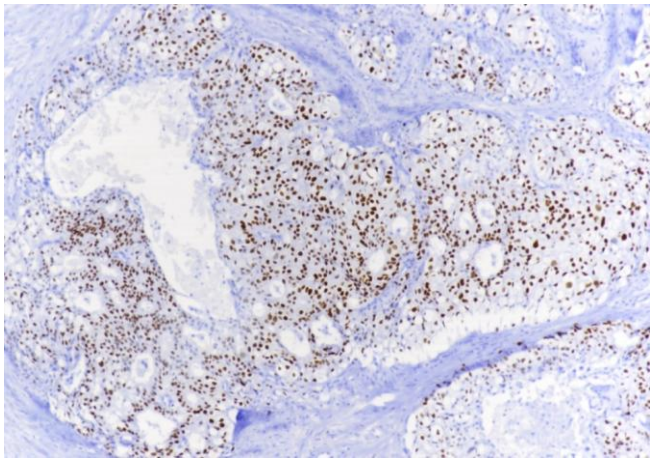

Fig. 10: *Prostatic Adenocarcinoma with Hypernephroid & Comedo pattern showing AR staining score 2+ (IHC stain, 100X magnification).*

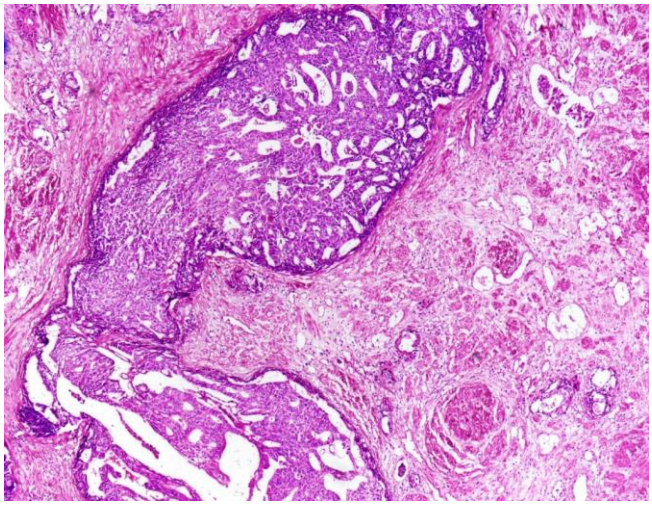

Fig. 11: *Cribriform pattern of Prostatic Adenocarcinoma with Gleason Score 9 (H & E stain, 40X magnification).*

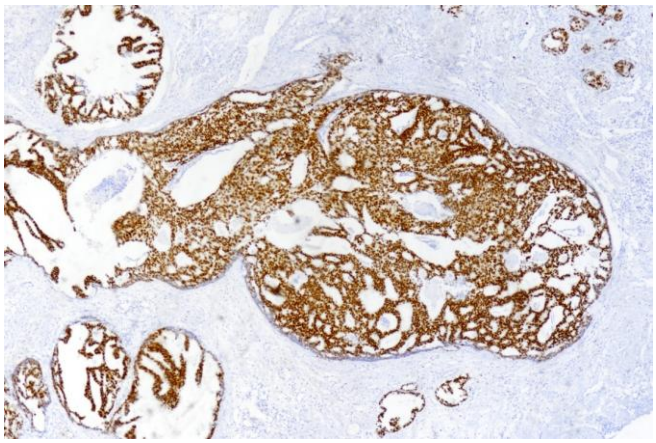

Fig. 12: *Cribriform pattern of Prostatic Adenocarcinoma showing AR staining score 3+(IHC stain, 40X magnification).*

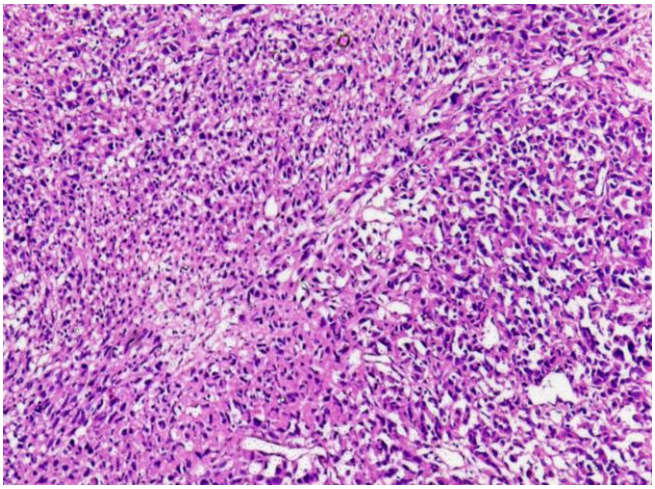

Fig. 13: *Prostatic Adenocarcinoma with Sarcomatoid Differentiation (Gleason Score = 10) (H & E stain, 200X magnification).*

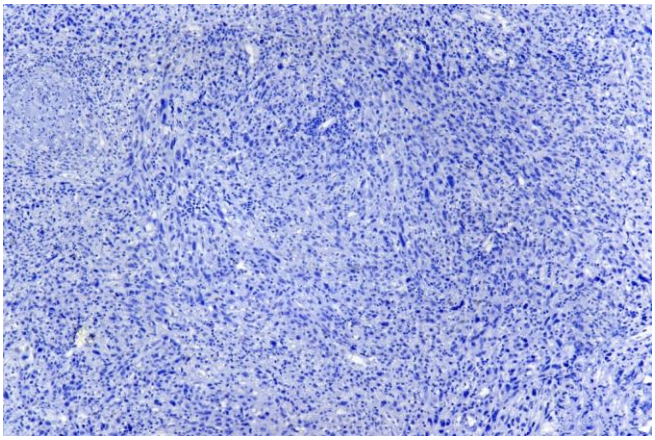

Fig. 14: *Same case of Prostatic Adenocarcinoma with Sarcomatoid Differentiation showing zero (0) AR staining Score (IHC stain, 100X magnification).*

DISCUSSION

Prostate cancer is the second commonest malignancy of males all over the world with the highest incidence in United States of America.[2] It is the fourth commonest cancer among males in Pakistan.[3] Its incidence in our country is 3.8% due to lower life expectancy and no screening methods. However, its risk is increasing here because of environmental and lifestyle factors, particularly tendency of urbanization and change in socioeconomic status. Etiology of prostate cancer is not well understood despite its high morbidity and mortality.[18] Increasing age is one well established risk factor.[5] Prostate carcinoma is a disease of old age and men younger than 40 years are less likely to be diagnosed with this malignancy. The average age for developing Prostate carcinoma is about 65 years and older.[2]

The age range of prostatic adenocarcinoma pati-

ents was found as 45 - 95 years with mean and standard deviation of 67.4 ± 11.3 years by Bhurgari et al (2009).[19] Another study conducted by Baek et al (2012) showed that the median age of patients with prostate carcinoma is 67.2 years with an age range of 49 to 80 years.[15] A similar study done in 2015, descrybed mean age and standard deviation of prostatic adenocarcinoma patients as 64.8 ± 10.3 years.[20] In our study the mean age of 60 patients which were diagnosed with prostatic adenocarcinoma was 67.33 ± 8.806 year with minimum and maximum age of 45 and 85 years which is almost similar as reported in other studies.[15,19,20]

Gleason scoring system is used to describe various architectural patterns seen in adenocarcinoma of prostate. Gleason score is a good prognostic factor for prostate cancer.[6,7,21] This study includes 60 diagnosed cases of adenocarcinoma of prostate with different Gleason scores. There were 7 (11.67%) patients who had Gleason score of 6, 5 (8.33%) patients had Gleason score of 7, 19 (31.67%) patients had Gleason score of 8, 26 (43.33%) patients had a Gleason score of 9 and 3 (5%) patients had Gleason score of 10. The mean Gleason score was 8.22 ± 1.075 with minimum and maximum Gleason score of 6 and 10. In a study by Zhang et al, 22 (16.8%) patients had Gleason score of 6, 46 (35.1%) patients had Gleason score of 7 and 63 (48.1%) patients had Gleason score of 8-10.[22] The results of the study by Baek et al (2012) showed 17 (25.7%) patients with Gleason score ≤ 6, 38 (57.6%) cases with Gleason score of 7 and 11 (16.7%) patients with Gleason score ≥ 8.[15]

Gleason score ≤ 6 is considered "low grade", 7 as "intermediate grade" and 8 - 10 as "high grade" prostate carcinoma.[7,14] According to these histological grades, 7 (11.67%) cases in this study had low grade (with Gleason score of 6), 5 (8.33%) had intermediate grade and 48 (80%) cases were classified into high grade tumor category. This can be comparable with the results of a study conducted by Wesam M. Osman et al (2013) in which prostatic adenocarcinoma cases were histologically classified into 24 cases (34.8%) of "low grade" carcinomas (with Gleason score of 6), 18 cases (26%) of "intermediate grade" carcinomas (with Gleason score of 7) and 27 cases (39%) of "high grade" carcinomas (with Gleason score of 8 and 9).[23]

The perineural invasion (PNI) is the presence of prostate cancer tracking around or along the nerve within the perineural space. It is a predictor of extraprostatic tissue extention of the tumor or ultimately recurrence of the tumor. Perineural invasion can be seen in high grade tumors.[24] Vargas So et al have shown perineural invasion in 16.7 % of patients and was related with high Gleason score.[25] Another study described PNI (perineural invasion) in 34% cases where it showed a significant association with higher Gleason scoring.[26] John O Delancey et al (2013) in their study has reported 20% positive perineural invasion in patients of prostatic carcinoma.[27] This study comprised of 60 cases of prostatic adenocarcinoma, out of which 27 (45%) cases showed positive perineural invasion while in remaining 33 (55%) cases, no perineural invasion was identified. Majority of the cases with positive perineural invasion were of high Gleason score (8-10). However, the comparison of high grade adenocarcinomas having positive perineural invasion with those having negative perineural invasion did not show any statistical significance.

The Androgens and Androgen Receptors have important roles both in the development of normal as well malignant prostate gland.[15,28] The intensity of AR staining on IHC is determined by assigning certain scores ranging from 0-3, where 0 means no staining, 1 means weak equivocal staining, 2 means unequivocal moderate staining and 3 represents strong staining.[23] In the current study the Androgen Receptor was detected in 59 cases (98.33%) and was not detected in only 1 case (1.67%) so its score was graded as 0. In cases with AR positivity, 6 cases (10%) have 1+ score, 24 cases (40%) had 2+ score and 29 cases (48.33%) had a score of 3+.

In the study by Baek et al (2012) AR expression was observed in 39 (59.1%) cases of prostatic adenocarcinoma of a total of 66. The expression of AR in their study was not correlated significantly with Gleason score.[15] In present study, seven out of sixty cases were of low grade (Gleason score 6), of which 2 cases, 2 cases and 3 cases showed weak = 1+, moderate = 2+ and strong staining intensity = 3+ respectively. Five cases represented intermediate grades (Gleason score 7) of which 3 cases showed weak = 1+, 2 cases showed strong staining intensity = 3+ while none of the cases showed moderate staining intensity = 2+. Both low and intermediate grades have not shown any case of negative or zero AR score. Forty eight cases out of a total of sixty cases were of high grade (Gleason score 8-10), of which only one case was labeled as AR negative or zero staining. These high grade cases showed staining scores as 0, 1+, 2+ and 3+ in 1case, 1 case, 22 cases and 24 cases respectively. The single case of AR negative was histologically classified as sarcomatoid variant of prostatic adenocarcinoma. The *p*-value was 0.001 showing significant association between AR scoring, Gleason score and histological grade.

According to results of Wesam M. Osman et al (2013), a significant inverse correlation was observed between AR expression in prostate cancer and tumor grade. But no such correlation was found in the current study. In the present study only one case was detected as AR-negative or zero staining. This AR negative case was graded as high grade prostatic adenocarcinoma (with the Gleason score of 10) and with sarcomatous change thereby supporting the evidence that certain men with the AR-negative prostatic carcinoma

have a worse prognosis compared to those with the AR-positive prostatic carcinoma.[23]

It is ***concluded*** that AR is a diagnostically useful marker for prostate adenocarcinoma. It was positive in 59 cases in this study. AR positivity is different in different grades of Prostate carcinoma. Tumors with high grades have shown strong positive expression for AR.

Gleason score and AR expression have shown direct relationship with each other.

AR immunomarker can be used to predict prognosis of patients with higher prostate carcinomas treated with Androgen Deprivation Therapy (ADT). Low expression of AR signifies less or no response to ADT.

Author's Contribution

GF: Substantial contribution to conception and design, acquisition of data, analysis and interpretation of data and drafting the article.
SN: Substantial contributions to conception and design, analysis and interpretation of data.
RJ: Drafting the article and revising it critically for important intellectual content.

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Conflict of Interest

Authors declare no conflict of interest.

Financial Disclosure

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