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ORGINAL ARTICLE

Clinicopathological Significance of Programed Death -Ligand -1(PD-L1) and Proliferation Cell Nuclear Antige(PCNA)Expression in Prostatic Carcinoma; an Immunohistochemical Study

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ABSTRACT

Background: Carcinoma of the prostate is the most diagnosed tumors and the second top reason of cancer-related deaths in American men,
The programmed death-ligand 1 (PD-1/PD-L1 pathway was a T-cell checkpoint pathway that sent repressing signals to T cells that can constrain immunity, PD-L1expression and relation to both pathological, clinical parameters and prognosis were studied in many cancers. proliferation cell nuclear antigen (PCNA)is proliferating cellular nuclear antigen, PCNA is an acidic nuclear protein, expressed mainly in phase S of the cellular cycle.We intended in this work to explore the immunohistochemical expression of PDL1 & (PCNA) in cancer prostate and correlate their expression with other clinicopathologic parameters. **Methods:** 46 cases of prostatic adenocarcinoma were collected from Pathology Department. Faculty of Medicine. Zagazig University between June 2018 to June 2020, using anti PDL1 & (PCNA) antibodies.**Results:** For PDL1 expression19 cases were positive (41.3%), showing membranous and cytoplasmic expression in tumor cells. Statistically significant relation was found between PDL1 expression and Age, grade, and stage, those who received chemotherapy. For PCNA expression 33 cases were positive (71.7%) showing nuclear expression. Statistically significant relation was found between PCNA expression and grade and stage and those who received chemotherapy. There is non-significant positive correlation between PDL-1 and PCNA.**Conclusions:** PDL1 may be a likely new marker or therapeutic goal for prostatic carcinoma cases, PCNA commonly used as a prognostic marker as an indicator of malignant cellular proliferation.

Keywords: PDL1; PCNA;immunohistochemistry; prostatic carcinoma

INTRODUCTION

Carcinoma of the prostate is the most diagnosed tumor, with an estimated 174,650 new cases and 31,620 deaths in 2019, in United States. Carcinoma of the prostate is the most common malignant tumor and the 2nd leading reason of cancer-related mortality in American men [1].The lethality of prostatic carcinoma is mainly due to locally advanced and particularly metastatic castration resistant diseases where no cure is available [2].In Egypt it represents the sixth most common cancer in male population after cancer of the liver, bladder cancer, lung cancer, non-Hodgkin lymphoma, and brain cancer [3].

Cancer of the prostate has various pathologic presentations and has a wide variety of clinical behavior, from a slow growing tumor, which has no clinical significance, to a highly aggressive, metastatic fatal illness [4].Many prognostic factors for prostatic carcinoma including Gleason score, preoperative level of (PSA) and some molecular markers[5].

The PD-1/PD-L1 pathway was a T-cell checkpoint pathway that sent inhibitory signals to T cells that can impede immunity [6].PD-L1, a PD-1 ligand named also B7 homolog 1 (B7-H1) or CD274, is identified in T lymphocytes, B Lmphocytes, dendritic cells, macrophages and several malignant cells [7].

PD-L1expression and relation to both pathological, clinical parameters and prognosis were studied in many cancers, but the exact mechanism of how PD-L1 and its effect on tumor microenvironments can have a role in cancer immunity is not adequately understood [8].

Anti-PD-1 and anti-programmed cell death-ligand 1 (PD-L1) treatment have been approved for the

treatment of Hodgkin's disease, desmoplastic melanoma, Merkel cell carcinoma, skin melanoma, non-small cell lung cancer, small cell lung cancer, head and neck malignant tumors, gastroesophageal malignancies, bladder & urinary tract malignant tumors, renal cell carcinoma, hepatocellular carcinoma, and any solid cancer with high-level of microsatellite instability [9].

Much novel research which evaluated the level of PD1/PDL1 expression and its prognostic role in primary prostatic carcinoma showed that PDL1 is independent factor for radical prostatectomy [10].

(PCNA) is proliferating cell nuclear antigen, PCNA is an acidic nuclear protein, expressed mainly in phase S of the cellular cycle. It becomes active, in various tissues especially in nervous tissue, as a first response to many hazards [11].

(PCNA) is the molecular coordinator for DNA replication and for preserving genome integrity, PCNA forms a homotrimeric sliding clamp that encircles the chromatin and functions as a molecular platform to aggregate proteins involved in DNA synthesis, cell-cycle control, and DNA harm response, and repair [12].

PCNA has been widely used as a tumor marker for cancer cell progression and patient prognosis [13].

METHODS

Our patients were conducted to pathology, urology, and clinical oncology departments. Faculty of Medicine, Zagazig University in collaboration with each other as from the period of June 2018 to June 2020 as a retrospective cohort study. At the pathology department, the research includes sections from formalin-fixed, paraffin-embedded samples from 46 patients Specimen sent, processed. Patients' data are collected from patients' records with approval by the local Ethical Committee. 0ur study included patient of any age proved pathologically to have prostatic adenocarcinoma of any stage. We excluded patients with other primary cancer or had received previous chemotherapy or hormonal therapy.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients underwent a proper history and examination. Investigations were requested in the form of lab profile and radiological studies such as pelviabdominal ultrasonography, chest x-ray also chest and pelviabdominal computed tomography. Bone scan and PET scan were requested according to clinical scenarios. All patients underwent cystoscopic diagnostic biopsy. All patients received hormonal therapy. Chemotherapy protocols were proposed for our patients who had biochemical failure.

Immunohistochemical staining

We used the streptavidin-biotin technique. Paraffin-embedded blocks have been cut into Four-micron thick sections; deparaffinization was complete in a sequence of xylene, and rehydration was done in downward rankings of alcohol, endogenous peroxidase activity was blocked by placing the part in 0.5% hydrogen peroxide in methanol for 10 min microwave antigen retrieval

For PDL1the slides were incubated for 30 min at room temperature with a rabbit monoclonal antibody to PDL1 (diluted 1:100, isotope IgG, Clone CAL10 1:100 dilution, Biocare medical 4040 Corporation, pike lane, concord, USA, Catalogue number 94520). And rabbit polyclonal PCNA antibody (dilution, 1:100; cat. no. ab18197); [14].

Immunohistochemical evaluation of both markers

For PDL1

PDL1 positive expression is assessed in both tumor cells and TILs (tumor infiltrating lymphocytes) in stroma of prostate. PDL1 positivity (membranous and or cytoplasmic) defined as ≥ 1 of viable tumor cells and as ≥ 1 of TILs. The expression of PDL1 in tumor cells was evaluated as follows: negative expression (<1%positive tumor cells, the positive expression was scored as low expression (≥ 1%-49% positive tumor cells), high expression (≥50% -100% positive tumor cells) [15].

For PCNA:

All staining was restricted to the nucleus of tumor cells and was demonstrated as partial, diffuse, and granular brown pattern. PCNA positivity was scored as following: staining of <20% of cells (-), 21–40% (+), 41–60% (++), 61–100% (+++). Nuclear PCNA, staining was positive if >21% and negative if <20% of cells stained [16].

Statistical analysis

All statistics were done through using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium). Shapiro-Wilk test, Mann Whitney U test, Kruskal Wallis H test, Chi-square test and Fisher's exact test were used. Survival was estimated using the method of Kaplan-Meier plot, test. P-value <0.05 was considered significance.

RESULTS

Immunohistochemical results:

For PDL1 expression19 cases were positive (41.3%), showing membranous and cytoplasmic expression in tumor cells.Statistically significant relation was found between PDL1 expression and Age, grade and stage.

For PCNA expression 33 cases were positive (71.7%) showing nuclear expression. Statistically significant relation was found between PCNA expression and garde and stage.

Immunohistochemical results:

For PDL1 expression19 cases were positive (41.3%), showing membranous and cytoplasmic expression in tumor cells..

For PCNA expression 33 cases were positive (71.7%) showing nuclear expression.

There is statistically significant association between PDL-1 expression and all of age, stage, Gleason score, and chemotherapy. Positive PDL-1 was associated with older age, stage IV, Gleason score≥7, T (WHO, 2016) and those who received chemotherapy. There is non-significant association between PDL and either presence of lymph node metastasis, distant metastasis, risk stratification, PSA level or radiotherapy. There is statistically significant association between PCNA expression and all of stage, Gleason score, T (WHO 2016) classification, and chemotherapy. Positive PCNA was associated with stage III, and IV, Gleason score≥7 and T8, and ≥9 those who received chemotherapy. There is non-significant association between PCNA and either age, presence of lymph node metastasis, distant metastasis, risk stratification, PSA level or radiotherapy.

There is statistically significant association between level of PDL-1, PCNA expression and patient mortality. Positive levels significantly associated with mortality. There is significant relation between overall mean survival in PDL-1 negative was 35.2 Months while that for PDL-1 positive was 33 months

There is non-significant positive correlation between PDL-1 and PCNA

Table(1): Baseline characteristics of the studied patients:

	N=46	%
Age:		
<60 years	21	45.7
≥ 60 years	25	54.3
Gleason grading:		
<7	21	45.7
7	14	30.4
>7	11	23.9
Staging:		
I	7	15.2
II	15	32.6
III	14	30.4
IV	10	21.7
T (WHO 2016):		
≤6	21	45.7
3+4	9	19.6
4+3	5	10.9
8	8	17.4
≥9	3	6.5
Lymph node metastasis:		
Negative	40	87.0
Positive	6	13.0
Distant metastasis:		
Negative	36	78.3
Positive	10	21.7
Risk stratification:		
Low	4	8.7
Intermediate	25	54.3
High	17	37.0
PSA:		
≤10	15	32.6
>10 – 20	25	54.3

	N=46	%
>20	6	13.0
PDL.1:		
Negative	27	58.7
Positive	19	41.3
PCNA:		
Negative	13	28.3
Positive	33	71.7
Hormonal treatment:		
Yes	46	100
Radiotherapy:		
Absent	15	32.6
Present	31	67.4
Chemotherapy:		
No	35	76.1
Yes	11	23.9
Death:		
No	33	71.7
Yes	13	28.3

Table(2): Relation between PDL1, PCNA expression in the studied patients and disease-specific characteristics:

	Total	PDL--1 Negative N=27 (58.7%)	Positive N=19 (41.3 %)	p#	Membranous PCNA expression: Negative N=13 (28.3%)	Positive N=33 (71.7%)	p#
Age group:							
<60 years	21	17(81.0)	4 (19.0)	0.005*	5 (23.8)	16 (76.2)	0.539
≥60 years	25	10(40.0)	15 (60.0)		8 (32.0)	17 (68.0)	
Stage:							
I	7	5 (71.4)	2 (28.6)	0.003*	4 (57.1)	3 (42.9)	
II	15	13 (86.7)	2 (13.3)		7 (46.7)	8 (53.3)	0.002*
III	14	7 (50.0)	7 (50.0)		2 (14.3)	12 (85.7)	
IV	10	2 (20.0)	8 (80.0)		0 (0)	10 (100)	
LN metastasis:							
Negative	40	22 (55.0)	18 (45.0)	**0.**377	12 (30.0)	28 (70.0)	0.659
Positive	6	5 (83.3)	1 (16.7)		1 (16.7)	5 (83.3)	
Distant metastasis:							
Negative	36	20 (55.6)	16 (44.4)	0.488	12 (33.3)	24 (66.7)	0.240
Positive	10	7 (70.0)	3 (30.0)		1 (10.0)	9 (90.0)	
Gleason score:							
<7	21	17 (81.0)	4 (19.0)		8 (38.1)	13 (61.9)	
7	14	6 (42.9)	8 (57.1)	**0.009***	5 (35.7))	9 (64.3)	**0.037***
>7	11	4 (36.4)	7 (63.6)		0 (0)	11 (100.0)	
T (WHO 2016):							
≤6	21	17 (81.0)	4 (29.0)		8 (38.1)	13 (61.9)	
3+4	9	3 (33.3)	6 (66.7)		3 (33.3)	6 (66.7)	
4+3	5	3 (60.0)	2 (40.0)	**0.024***	2 (40.0)	3 (60.0)	**0.04***
8	8	3 (37.5)	5 (62.5)		0 (0.0)	8 (100.0)	
≥9	3	1 (33.3)	2 (66.7)		0 (0.0)	3 (100.0)	
Risk stratification:							
Low	4	2 (50)	2 (50)		2 (50.0)	2 (50.0)	0.158
Intermediate	25	18 (72.0)	7 (28.0)	0.204	8 (32.0)	17 (68.0)	
High	17	7 (41.2)	10 (58.8)		3 (17.6)	14 (82.4)	

	Total	PDL--1 Negative N=27 (58.7%)	Positive N=19 (41.3 %)	p#	Membranous PCNA expression: Negative N=13 (28.3%)	Positive N=33 (71.7%)	p#
PSA:							
<10	15	9 (60.0)	6 (40.0)		5 (33.3)	10 (66.7)	0.466
10 – 20	25	13 (52.0)	12 (48.0)	0.557	7 (28.0)	18 (72.0)	
>20	6	5 (83.3)	1 (16.7)		1 (16.7)	5 (83.3)	
Radiotherapy:							
Absent	15 ()	9 (60.0)	6 (40.0)	0.901	6 (40.0)	9 (60.0)	0.219
Present	31 ()	18 (58.1)	13 (41.9)		7 (22.6)	24 (77.4)	
Chemotherapy:							
Absent	35	25 (71.4)	10 (28.6)	**0.004***	13 (37.1)	22 (62.9)	0.02*
Present	11	2 (18.2)	9 (81.8)		0 (0.0)	11 (100.0)	

*p<0.05 is statistically significant #Chi square test **p≤0.001 is statistically highly significant
PSA (prostatic specific antigen)

Table (3) : Correlation between the studied markers:

	PDL-1	
	Phi	**p**
PCNA	0.232	0.115

There is non-significant positive correlation between PDL-1 and PCNA

Table (4): Kaplan– Meier survival curves illustrating survival time differences in patients as regard markers expressions

		Total N	N of Events	Censored		Survival time, Months				P
				N	%	Mean		Median		
						Estimate ±SD	95% CI	Estimate ±SD	95% CI	
PDL-1	Negative	27	2	25	92.6%	35.2±0.6	34.1-36.2			0.001*
	Positive	19	11	8	42.1%	33.0±0.7	31.6-34.4	34.0± 2.2	29.7-38.3	
PCNA	Negative	13	0	13	100%					0.011*
	Positive	33	13	20	60.6%					
Overall		46	13	31	60.6%	34.8±0.5	33.4-35.2			

Table (5) : Cox regression analysis of factors significantly associated with mortality among the studied patients:

	β	p	Adjusted hazard ratio	95.0% CI Lower	Upper
PDL1 expression (+ve)	1.806	.435	6.088	.065	568.434
PCNA (-ve)	-11.111	.901	.000	.000	
Risk stratification(low)		.122			
Risk stratification(intermediate)	-4.589	.097	.010	.000	2.279
Risk stratification(high)	2.024	.324	7.567	.136	421.382
Chemotherapy (yes)	5.114	.007	166.272	3.978	6950.056
T (≥9)		.646			
T (≤6)	-6.555	.154	.001	.000	11.691
T (3+4)	-1.838	.371	.159	.003	8.885

	β	p	Adjusted hazard ratio	95.0% CI Lower	Upper
T (4+3)	-4.500	.154	.011	.000	5.363
T (8)	-2.140	.208	.118	.004	3.286
Stage I		.412			
Stage II	9.112	.948	9067.603	.000	3.77 (10^{121})
Stage III	3.643	.979	38.189	.000	1.766 (10^{120})
Stage IV	.727	.996	2.068	.000	1.070 (10^{119})
Gleason grading		.			
Age (≥60 years)	-.666	.703	.514	.017	15.830

Table(ST1): Correlation between the studied markers and death

	Total	PDL-1			PCNA		
		Negative	**Positive**	**p#**	**Negative**	**Positive**	**p#**
		N=27 (%)	**N=19(%)**		N=13(%)	**N=33(%)**	
Death:							
Yes	**33**	25(75.8)	8 (24.2)	**<0.001***	13 (39.4)	20 (60.6)	**0.009***
No	**13**	2 (15.4)	11 (84.6)		0 (0.0)	13 (100.0)	

*

*p<0.05 is statistically significant #Chi square test

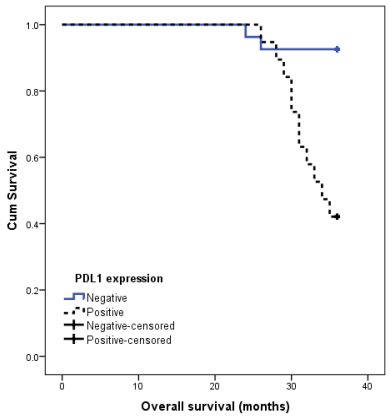

Figure (1): Kaplan Meier plot survival and PDL-1 expression (showing significant relation between overall mean OS in PDL-1 negative was 35.2 Months while that for PDL-1 positive was 33 months)

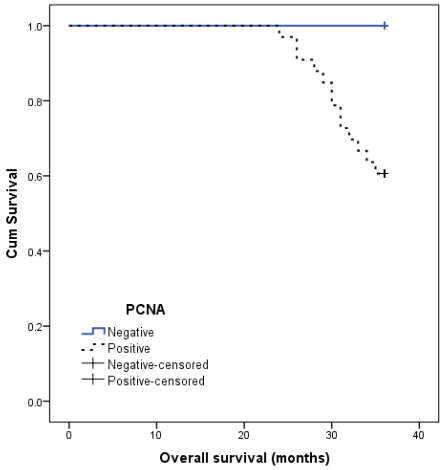

Figure (2): Kaplan Meier plot showing significant relation between overall survival and PDL-1 expression (p<0.05)

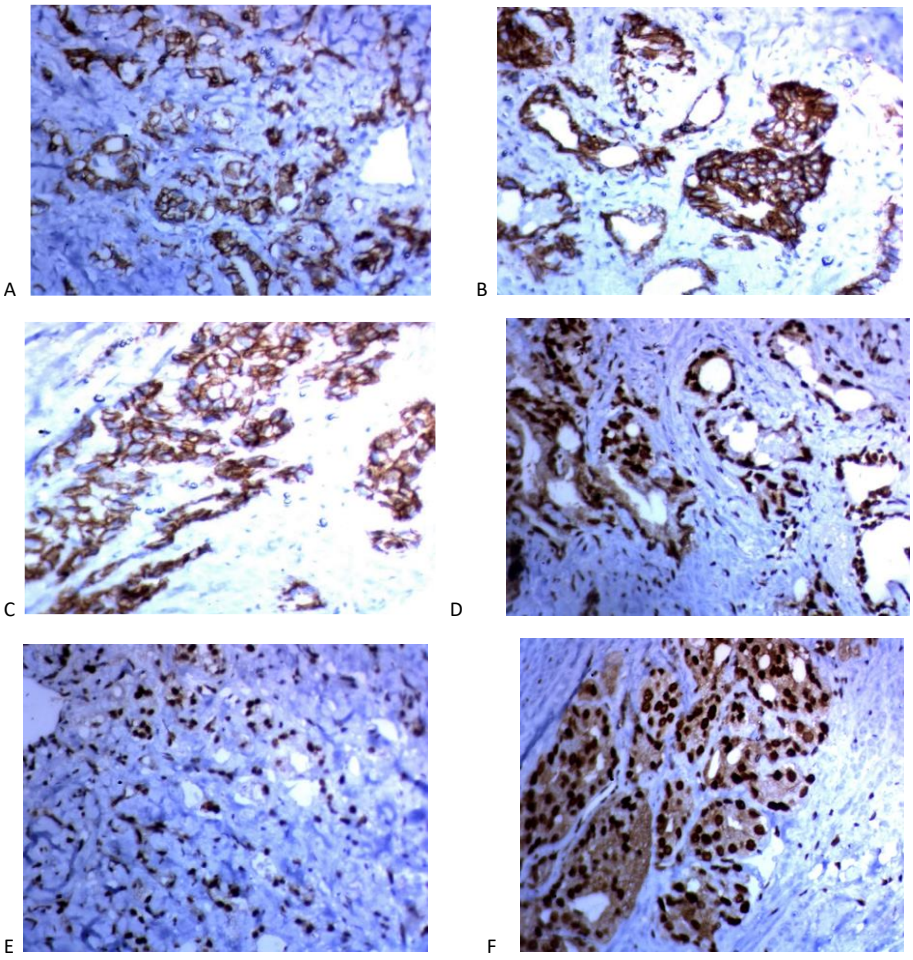

Figure (2) Immunohistochemical expression of PDL-1 and PCNA

A-Prostatic adenocarcinoma, Glesson score 6 (3+3) showing weak PDL-1 immunostaining (ABC x 200)
B) Prostatic adenocarcinoma, Glesson score 7 (3+4) showing strong PDL-1 immunostaining (ABC x 200)
C) Prostatic adenocarcinoma, Glesson score 8 (4+4) showing strong PDL-1 immunostaining (ABC x 200)
D) Prostatic adenocarcinoma, Glesson score 7 (3+4) showing moderate PCNA immunostaining (ABC x 400)
E) Prostatic adenocarcinoma, Glesson score 9 (5+4) showing strong PCNA immunostaining (ABC x 200)
F) Prostatic adenocarcinoma, Glesson score8 (4+4) showing strong PCNA immunostaining (ABC x 400)

DISCUSSION

Antibody-mediated blockade of the PD-1/PD-L1 axis is efficient in multiple solid tumors. Many studies have verified only restricted or no therapeutic activity ofPD-1eblocking therapies in cancer prostate; however, several studies presently are studying the utilization of such therapies in prostatic carcinoma [17].

In the current study we found PDL1 expressed in 19 /46 of cases (41.3%), showing membranous and cytoplasmic expression in tumor cells. In the study made by Li., etal [18]PDL1 was expressed in 49.6% (63/127), but in the study made by Sharma., etal [15] PDL1 was expressed in 13% of tumor cells. Also, in the study made by Haffner., et al [19] PDL1 was expressed only in 7.7 % in tumor cells, in the study made by Ness., etal [20]PDL1 was expressed in 92% of prostatic tumor cells. This variation in different studies may related to different monoclonal antibodies. In our study we found There is statistically significant association between PDL-1 expression and all of age(p=0.005), stage(p=0.003), Gleason score(p=0.009) ,this is in agree with the study made by Xian P., [21] and Haffner., etal [19] who found statistically significant association between PDL-1 expression and all of age, stage, Gleason score, also in the study made by Calagua,, etal., [22] PDL-1 expression was significantly association with Gleason score. but in contrary to what reported by Sharma., etal [15]who failed to find statistically significant association between PDL-1 expression and all of age, stage, Gleason score, also no significant relation between PDL-1 expression and all of age, stage in another study made by Baas., etal [23]and by Li., etal [18].

As the growth rate of tumor tissue is determined by proliferative activity and cell death, expression of PCNA as a proliferation marker in prostatic carcinoma were evaluated in current study .

As regard PCNA expression in the current study 33 /46 cases (71.7%) were positive showing nuclear expression. In the study made by Bantis., etal [16]PCNA was expressed in 85.7 % of cases of cancer prostate but in the study made by Zhong., etal [24]PCNA was expressed in 64.46 % of PCa cells.

In the current study we found a statistically significant association between PCNA expression and all of stage (p=0.002) , Gleason score(p=0.037) , T (WHO 2016) classification (p=0.04) classification (WHO 2016 classification was to include cribriform, fused, and poorly formed glands into Gleason pattern 4 and also differentiate the GS 7 into two PGGs (3 + 4 and 4 + 3) , this is in agree with Bantis., [16] who found statistically significant association between PCNA expression and all of stage and Gleason, as the expression of PCNA increased in high grade and stage and consider it as bad prognostic marker .Also in the study made by Zhong., etal [24]who found a statistically significant association between PCNA expression and stage, but in contrary to what reported by Wang., et al [25] who failed to find statistically significant association between PCNA expression and prostate cancer.

Although Meenal etal [26] found no significant association between PD-1/ PDL1 expression in tumor cells or tumor infiltrating lymphocytes our study revealed that mean overall survival in those with negative PDL-1 expression was 35.2 months which was significantly higher than that in those with PDL-1 positive expression (mean OS; 33 months).

There is statistically significant association between OS and membranous PCNA expression. All patients with positive PCNA died.

Bantis A etal [27] demonstrated that p120, Ki-67 and PCNA expression had significant prognostic value for disease-free survival, However, a higher recurrence was noted for those patients who had low expression (+) compared with those who had high expression (++ or +++).

Heng Li et al showed that. The median biochemistry recurrence (BCR)-free survival in PDL1-high/PD1-negative expression patients was 16 months (95% CI: 13.527-18.213), while PDL1-high/PD1-positive or PDL1-low/PD1-negative expression patients was 72.5months (95% CI: 28.957-116.103).

In metastatic disease, BCR-free survival was not significantly associated with PDL1/PD1 status. Of note, no PDL1-low/PD1-positive expression patients occurred High-PDL1 expression was significantly associated with lower BCR-free survival both in PD1-positive and PD1-negative (p=0.0193) and PD1-negative patients (p<0.0001) [28].

Conclusions and Recommendation : PDL1 may be a likely new marker or therapeutic goal for prostatic carcinoma cases , PCNA commonly used as a prognostic marker as an indicator of malignant cellular proliferation

Conflicts of interest: There are no conflicts of interest.

Financial Disclosures: No

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