

## Immunohistochemical Expression of Cyclin D1 in Prostate Carcinoma

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### ABSTRACT:

#### BACKGROUND:

Prostate carcinoma is one of the most common malignant tumors in men older than 50 years of age and is characterized by a highly variable clinical course. Cyclin D1 proto-oncogene is an important regulator of G1 to S phase progression in many different cell types

#### AIM OF STUDY:

To study the expression of cyclin D1 in prostate adenocarcinoma, and to evaluate the relationship of this protein with clinicopathological features (histological grade, perineural invasion, and preoperative PSA level).

#### MATERIALS AND METHODS :

This is retrospective study including 50 cases, forty cases diagnosed histopathology as prostate adenocarcinoma and 10 cases as a benign prostatic hyperplasia. These cases were collected from laboratory department of AL Shaheed Ghazi ALhariri hospital from November 2018 to May 2019. Type of biopsy is a needle core biopsy.

#### RESULTS:

The immunohistochemical expression of cyclin D1 was negative in benign prostatic hyperplasia, while in prostate adenocarcinoma 52.5% were positive .There was significant correlation between histological grade of prostate adenocarcinoma and immunohistochemical expression of cyclin D1 There was no association between immunohistochemical expression of cyclin D1 in prostate adenocarcinoma with the presence of perineural invasion, and the pre –operative PSA level.

#### CONCLUSION:

Cyclin D1 expressed in prostate carcinoma and not in benign prostate hyperplasia.

**KEYWORDS:** cyclin D1 expression , Prostate carcinoma .

### INTRODUCTION:

Prostate adenocarcinoma is considered the most common solid neoplasm in Europe, it represents 22.8 % of all recently diagnosed cancer cases among men <sup>(1)</sup>This may be attributed to the use of prostatic specific antigen (PSA) in early detection of prostate carcinoma at early stages<sup>(1)(2)</sup> . Prostate cancer is 4<sup>th</sup> from the most common ten cancer in Iraq (according incidence rate (per 100,000 population) of top ten cancer in Iraq, 2016). Prostatic carcinoma increases with age, from less than 10% in men 40 to 50 years of age to more than 70% in those older than 80 years<sup>(3)</sup>. Prostate carcinoma occurs in black about one and a half those of white males <sup>(4)</sup>. 5% to 10% of prostatic carcinomas have a genetic link. If one of the first degree relative had prostate carcinoma, risk of developing the disease is two to three times greater than average<sup>(5)</sup>.

Cyclin D1 proto-oncogene is an important regulator of G1 to S phase progression in many different cell types <sup>(6)</sup>.Prostate carcinoma is characterized by alterations in cell-cycle regulatory pathways. Defects in the expression of cyclin D1, a key cell-cycle regulator, have been implicated in progression of various types of cancer including prostate carcinoma<sup>(7)</sup>.

#### MATERIALS AND METHODS:

This is a retrospective study including 50 cases; forty cases are diagnosed histopathology as prostate adenocarcinoma and 10 cases as a benign prostatic hyperplasia served as a control in this study. These cases were collected from laboratory department of AL Shaheed Ghazi ALhariri hospital from November 2018 to May 2019 .Type of biopsy : Needle core biopsy .

Five microns sections were obtained from formalin fixed –paraffin embedded tissue blocks and mounted on Pathn Situ positively charged slides.

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### Evaluation of immunostaining:

Immunohistochemical expression of cyclin D1 in prostatic adenocarcinoma should be heterogenous brown nuclear staining and is better evaluated by percentage of positive cells as to classify the results as: Less than or equal to 5% of tumor cells are considered negative and More than 5% of tumor cells are considered positive<sup>(7)</sup>.

Colonic adenocarcinoma is considered as a positive control tissue in this study

### RESULTS:

This study deals with fifty cases; forty of them were diagnosed as prostate adenocarcinoma; while the other ten cases were benign prostatic hyperplasia.

#### 1 .Cyclin D1 expression in benign prostatic hyperplasia:

All cases (ten)(20%)were negative for cyclin D1 and some of these cases showed positivity for cyclin D1 in stromal cells only (non –specific reaction).

#### 2. Correlation of cyclin D1 expression in prostate adenocarcinoma according to the studied parameters:

##### 2.1 Relation of histology to age

Table 1: Relation of histology to age.

	Low grade prostate adenocarcinoma N=10 Mean± SD	High grade prostate adenocarcinoma N =30 Mean ± SD	P -value
Age (yr)	59.38± 13.54	62.67± 4.18	0.264

##### 2.2 Correlation of cyclin D1 expression with histological grade of tumor:

There was significant statistical correlation between histological grade of prostatic

adenocarcinoma and immunohistological expression of cyclin D1 at P- value is 0.0018.

As shown in table (2).

Table 2: Relation of cyclin D1 expression to histological grade.

Gleason grade	CyclinD1 >5% (positive)	CyclinD1 <5% (negative)	Total	P-value = 0.0018
Low grade	1 (5.25%)	9 (4.75%)	10	
High grade	20 (15.75%)	10 (14.25%)	30	
Total	21	19	40	

##### 2.3 Correlation of cyclin D1 expression and prineural invasion :

There is NO significant statistical correlation between presence of perineural invasion and

immunohistochemical expression of cyclin D1 with P- value is 0.3701, as shown in table (3).

Table 3: Relation of cyclin D1 expression to perineural invasion.

Perineural invasion	CyclinD1 <5% (negative)	CyclinD1 >5% (positive)	Total	P-value =0.3701
Positive	11 (42.3%)	15(57.69%)	26	
Negative	8 (57.14%)	6(42.85%)	14	
Total	19	21	40	

##### 2.4 Correlation of Cyclin D1 expression and preoperative PSA level:

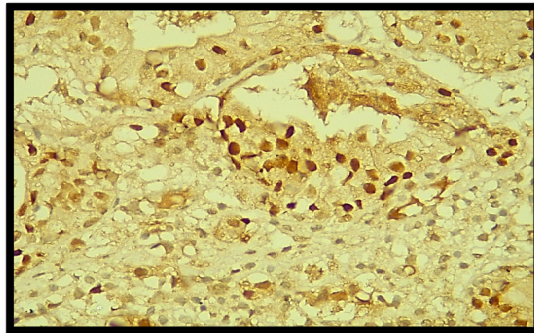
There is NO significant statistical correlation between the preoperative PSA level and

immunohistochemical expression of cyclin D1 with P value is 0.5394 , as shown in table(4).

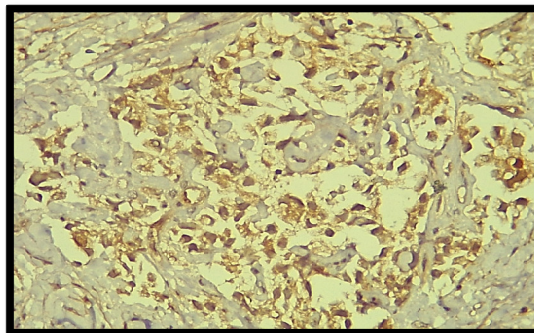
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**Table 4: Relation of cyclin D1 expression and preoperative PSA level.**

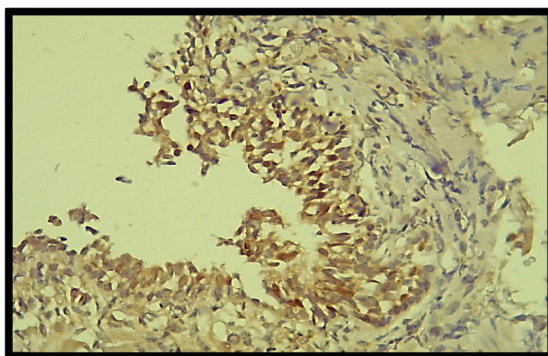
Pre operative PSA level	Cyclin D1 <5% (negative)	Cyclin D1 >5% (positive)	Total	P-value= 0.5394
PSA <4 ng/ml	5 (41.66%)	7(58.33%)	12	
PSA 4-10 ng/ml	7(38.88%)	11(61.11%)	18	
PSA >10 ng/ml	6(60.00%)	4 (40.00%)	10	
Total	18	22	40	



**Figure 1:Prostate adenocarcinoma (core biopsy) ,grade 4 adenocarcinoma with perineural invasion showing positive nuclear staining for cyclin D1(IHC)(X40).**



**Figure 2:Prostate adenocarcinoma (core biopsy) ,high grade adenocarcinoma showing positive nuclear staining for cyclin D1 (IHC)(X40).**



**Figure 3: Prostate adenocarcinoma (core biopsy) ,low grade adenocarcinoma showing positive nuclear staining for cyclin D1 (IHC)(X40).**

**DISCUSSION:**

Prostate specific antigen (PSA) is considered a nonspecific biomarker for prostate cancer. This study showed a negative statistical correlation between pre-operative PSA levels and cyclin D1 expression in prostate adenocarcinoma, thereby supporting the theory that PSA levels are not associated with cell cycle disorders in prostate carcinoma<sup>(6)</sup>. The results agree with **Pereira et al.** <sup>(7)</sup>, and **Han et al.** also<sup>(8)</sup>, both showed negative statistical correlation between PSA level and Immunohistochemical expression of cyclin D1. Results in this study disagree with **Nakamura et al.** at 2013 that have found statistically significant positive correlations of cyclin D1 expression and PSA levels <sup>(9)</sup>. The heterogeneous pattern of cyclin D1 immunostaining showed in this study is in agreement with the results of **Han et al.** (1998) supporting the hypothesis that many different mechanisms are involved in prostate carcinogenesis <sup>(8)</sup>. In this study, we found a positive statistically significant correlation between the Gleason grade of prostate adenocarcinoma and cyclin D1 expression, with high-grade tumors displaying high cyclin D1 expression compared with low-grade tumors, in agreement with a study conducted by **Ahmed ES et al.** (2020) who showed 97.5% of cases positive for cyclin D1 <sup>(10)</sup>, **EminOzbek et al.** (2000) who showed 100% of cases positive for cyclin D1<sup>(11)</sup>, and **Pereira RA et al** (2014). There is another study by **Drobnjak M et al** (2000), in this study no significant correlation between tumor grade and immunohistochemical expression of cyclin D1 may be related to tumor heterogeneity<sup>(12)</sup>. This variation may be related to many factors as type of biopsy, sample size, method of immunohistochemical staining (we use manual staining, while outside they use autostaining) and tumor heterogeneity. Regarding the other parameter which is the presence of Perineural invasion, perineural invasion is considered as an aggressive histological marker in prostate adenocarcinoma. This study showed a negative statistical correlation between this histological feature and cyclin D1 expression, which was unlike **Pereira RA et al** (2014)<sup>(7)</sup>, **Ozbek E et al** (2000)<sup>(11)</sup>, **Nakamura Y et al** (2013)<sup>(9)</sup>, all of them showed significant statistical correlation between the presence of perineural invasion and the nuclear expression of cyclin D1, which means the expression of cyclin D1 in prostate carcinoma might be a potential marker of aggressiveness in prostate carcinoma and

correlate with poor prognosis. The results in this study are similar to the study by **Drobnjak M et al** (2000) <sup>(12)</sup>. This difference between our result and the others study may be related to sample size and type of biopsy.

**CONCLUSION:**

The variable expression of cyclin D1 in prostatic adenocarcinoma and Absence of its expression in benign prostatic hyperplasia. There was a significant statistical correlation between histological grade and immunohistochemical expression of cyclin D1. High expression of cyclin D1 in high grade prostate adenocarcinoma than low grade tumors. There was no significant statistical correlation between cyclin D1 expression and other parameters (preoperative PSA level and perineural invasion).

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