

# CYCLIN D<sub>1</sub> EXPRESSION IN PROSTATIC CARCINOMA

## THESIS

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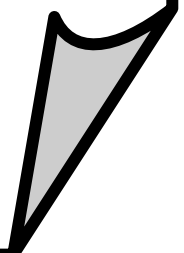
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## ABSTRACT

Prostatic carcinoma is a common and growing public health problem. Cyclin D<sub>1</sub> is a cell regulatory protein, which is believed to play an important role in both tumorigenesis and grading of many cancers. The role of Cyclin D<sub>1</sub> as a prognostic factor in cancer prostate is controversial.

The present study was done on a total of forty cases of prostatic carcinoma removed by radical prostatectomy. Immunohistochemical expression of Cyclin D<sub>1</sub> was evaluated in all cases. Correlation between the intensity of Cyclin D<sub>1</sub> expression and patient's age, serum PSA level, PIN, Gleason grades, Gleason scores and stages of prostatic carcinoma was evaluated.

All cases (100%) revealed foci (>10 % of cancer cells) with positive nuclear staining for Cyclin D<sub>1</sub> with different grades of intensity ranging from moderate to strong, while positive Cyclin D<sub>1</sub> expression was observed in the nuclei of PIN of 30 cases with grades of intensity ranging from weak to strong. No significant correlation was found between the intensity of Cyclin D<sub>1</sub> expression and patient's age, PIN, Gleason grades, Gleason scores or stages of prostatic carcinoma, while a significant correlation between intensity of expression of Cyclin D<sub>1</sub> and preoperative serum PSA level was observed.

Cyclin D<sub>1</sub> expression might affect PSA expression, which is considered an important tumor marker. Cyclin D<sub>1</sub> plays an important role in the pathogenesis and evolution of prostate cancer rather than the prognosis, thus Cyclin D<sub>1</sub> is not a reliable prognostic factor in cancer prostate.

**Key words:** Cyclin D<sub>1</sub>-Prostatic carcinoma.

# CONTENTS

<b>Introduction &amp; Aim of the Work .....</b>	<b>1</b>
<b>Review of Literature.....</b>	<b>4</b>
• <b>Anatomy of the prostate.....</b>	<b>4</b>
• <b>Histology of the prostate.....</b>	<b>7</b>
• <b>Prostatic carcinoma.....</b>	<b>9</b>
• <b>Gleason grading of prostatic carcinoma.....</b>	<b>18</b>
• <b>Histological variants of prostatic adenocarcinoma.....</b>	<b>24</b>
• <b>Carcinoma with spindle cell differentiation.....</b>	<b>27</b>
• <b>Prostatic intraepithelial neoplasia.....</b>	<b>28</b>
• <b>Ductal carcinoma.....</b>	<b>32</b>
• <b>Urothelial tumors.....</b>	<b>34</b>
• <b>Squamous tumors.....</b>	<b>35</b>
• <b>Basaloid and adenoid cystic carcinomas.....</b>	<b>35</b>
• <b>Mimickers of prostatic acinar adenocarcinoma.....</b>	<b>37</b>
• <b>Staging of prostatic carcinoma.....</b>	<b>52</b>
• <b>Prognostic factors of prostatic carcinoma.....</b>	<b>58</b>
• <b>Immunohistochemistry of prostatic carcinoma.....</b>	<b>61</b>
• <b>Cyclin D1.....</b>	<b>63</b>
<b>Materials &amp; Methods.....</b>	<b>65</b>
<b>Results .....</b>	<b>68</b>
<b>Discussion .....</b>	<b>96</b>
<b>Summary .....</b>	<b>102</b>
<b>Conclusion &amp; Recommendation.....</b>	<b>105</b>
<b>References .....</b>	<b>106</b>
<b>Arabic Summary .....</b>	

## LIST OF ABBREVIATION

<b>AJCC-UICC</b>	American Joint Committee on Cancer Classification- International Union Against Cancer
<b>AMACR</b>	Alpha methyl acyl Co-A Racemase
<b>BPH</b>	Benign prostatic hyperplasia
<b>CDK</b>	Cyclin dependant kinase
<b>CK</b>	Cytokeratin
<b>cT</b>	Clinical tumor staging
<b>cTNM</b>	Clinical Tumor, Node, Metastases staging
<b>DRE</b>	Digital rectal examination
<b>HGPIN</b>	High grade prostatic intraepithelial neoplasia
<b>hK2</b>	Human glandular kallikrein 2
<b>HMWCK</b>	High molecular weight cytokeratin
<b>LGPIN</b>	Low grade prostatic intraepithelial neoplasia
<b>LNcaP</b>	Prostate cancer cell lines
<b>MVD</b>	Microvessel density.
<b>PAP</b>	Prostatic acid phosphatase
<b>PIN</b>	Prostatic intraepithelial neoplasia
<b>pM</b>	Pathological metastases staging
<b>pN</b>	Pathological Node staging
<b>pRb</b>	Retinoblastoma protein
<b>PSA</b>	Prostate specific antigen
<b>PSMA</b>	Prostate specific membrane antigen
<b>pT</b>	Pathological Tumor staging
<b>pTNM</b>	Pathological Tumor, Node, Metastases staging
<b>SMA</b>	Smooth muscle actin
<b>SPSS</b>	Statistical Package for the Social Science
<b>TRUS</b>	Transrectal ultrasound
<b>TURP</b>	Transurethral resection of the prostate
<b>WHO</b>	World Health Organization

## LIST OF TABLES

<b>Tables</b>		<b>Pages</b>
<b>1</b>	Criteria for diagnosis of prostatic carcinoma	<b>16</b>
<b>2</b>	Description of nine basic patterns comprising the Gleason Grading System	<b>19</b>
<b>3</b>	Histopathological grading of prostatic carcinoma	<b>20</b>
<b>4</b>	Gleason Grading of Prostate Carcinoma subtypes	<b>22</b>
<b>5</b>	PIN diagnostic criteria	<b>30</b>
<b>6</b>	Major growth patterns of adenocarcinoma	<b>37</b>
<b>7</b>	Benign mimickers in relation to major growth patterns of prostatic adenocarcinoma	<b>38</b>
<b>8</b>	Atypical adenomatous hyperplasia vs well differentiated adenocarcinoma	<b>47</b>
<b>9</b>	Primary tumor, clinical (cT) staging, (2002 revision)	<b>53</b>
<b>10</b>	Comparison between TNM and whit more-jwette staging systems	<b>55</b>
<b>11</b>	Stage grouping of prostatic carcinoma	<b>57</b>
<b>12</b>	Important immunohistochemical stains in the diagnosis of prostate carcinoma	<b>62</b>
<b>13</b>	Age distribution in the studied cases	<b>68</b>
<b>14</b>	Distribution of cases according to their age	<b>69</b>
<b>15</b>	Distribution of cases according to their preoperative serum PSA level	<b>70</b>
<b>16</b>	Distribution of cases with PIN in relation to Gleason score of adjacent cancer	<b>71</b>
<b>17</b>	Distribution of cases according to Gleason grade	<b>73</b>
<b>18</b>	Distribution of cases according to Gleason score	<b>74</b>
<b>19</b>	Distribution of cases with Gleason score 7	<b>75</b>

<b>20</b>	Distribution of cases according to their Gleason score	<b>76</b>
<b>21</b>	Distribution of cases according to the pathological stage	<b>77</b>
<b>22</b>	Distribution of cases according to the pathological stage	<b>79</b>
<b>23</b>	Distribution of intensity of Cyclin D1 expression among studied cases	<b>80</b>
<b>24</b>	Cyclin D1 expression in foci of PIN	<b>81</b>
<b>25</b>	Relation between intensity of Cyclin D1expression and age	<b>82</b>
<b>26</b>	Relation between intensity of Cyclin D1expression and Serum PSA level	<b>83</b>
<b>27</b>	Relation between intensity of Cyclin D1expression and Gleason Score	<b>84</b>
<b>28</b>	Relation between intensity of Cyclin D1 expression and Pathological stage	<b>85</b>

## LIST OF GRAPHS

<b>Graphs</b>	<b>Pages</b>
<b>1</b> Age distribution in the studied cases	<b>68</b>
<b>2</b> Distribution of cases according to their age	<b>69</b>
<b>3</b> Distribution of cases according to their preoperative serum PSA	<b>70</b>
<b>4</b> Distribution of cases with PIN in relation to Gleason score of adjacent cancer	<b>72</b>
<b>5</b> Distribution of cases according to Gleason grade	<b>73</b>
<b>6</b> Distribution of cases according to Gleason scores	<b>74</b>
<b>7</b> Distribution of cases with Gleason score 7	<b>75</b>
<b>8</b> Distribution of cases according to their Gleason score	<b>76</b>
<b>9</b> Distribution of cases according to the pathological stage	<b>78</b>
<b>10</b> Distribution of intensity of Cyclin D1 expression among studied cases	<b>80</b>
<b>11</b> Cyclin D1 expression in foci of PIN	<b>81</b>
<b>12</b> Relation between intensity of Cyclin D1 expression and age	<b>82</b>
<b>13</b> Cyclin D1 expression according to Serum PSA level	<b>83</b>
<b>14</b> Relation between intensity of Cyclin D1 expression and Gleason Score	<b>84</b>
<b>15</b> Relation between intensity of Cyclin D1 expression and Pathological stage	<b>85</b>



## LIST OF FIGURES

<b>Figures</b>		<b>Pages</b>
<b>1</b>	Prostatic adenocarcinoma pattern 3 (rounded and angulated glands with moderate nuclear anaplasia and moderate desmoplasia) + PIN (H & E x200)	<b>86</b>
<b>2</b>	Prostatic adenocarcinoma pattern 3 (rounded and angulated glands) & pattern 4 (fused glands) + PIN. (H & E x200)	<b>86</b>
<b>3</b>	Prostatic adenocarcinoma pattern 4 (irregular cribriform pattern) + pattern 3 (rounded and angulated glands). Tumor cells showing moderate nuclear anaplasia with large nuclei showing nucleoli. (H & E x400)	<b>87</b>
<b>4</b>	Prostatic adenocarcinoma pattern 4 showing fused glands + pattern 3 showing rounded and angulated glands. (H & E x100)	<b>87</b>
<b>5</b>	Prostatic adenocarcinoma pattern 4 showing glomeruloid pattern + pattern 3 showing rounded and angulated glands. (H & E x400)	<b>88</b>
<b>6</b>	Prostatic adenocarcinoma pattern 4, Tumor cells having clear cytoplasm "Hypernephroid pattern". (H & E x400)	<b>88</b>
<b>7</b>	Prostatic adenocarcinoma pattern 4 with Signet cell ring feature. (H & E x400)	<b>89</b>
<b>8</b>	Prostatic adenocarcinoma pattern 5 with solid masses showing central necrosis "Comedo carcinoma". (H & E x400)	<b>89</b>
<b>9</b>	Prostatic adenocarcinoma Gleason score 4+3 with ganglion invasion. (H & E x400)	<b>90</b>
<b>10</b>	Prostatic adenocarcinoma Gleason score 3+3 with perineural invasion. (H & E x400)	<b>90</b>

<b>11</b>	Prostatic adenocarcinoma pattern 3 & adjacent PIN, both showing moderate nuclear Cyclin D1 staining, grade 2. (Cyclin D1 x100)	<b>91</b>
<b>12</b>	PIN showing strong nuclear Cyclin D1 staining, grade 3 (Cyclin D1 x400)	<b>91</b>
<b>13</b>	Prostatic adenocarcinoma pattern 4 with glomeruloid feature showing moderate nuclear Cyclin D1 staining, grade 2. (Cyclin D1 x400)	<b>92</b>
<b>14</b>	Prostatic adenocarcinoma pattern 4 with fused acini showing moderate nuclear Cyclin D1 staining, grade 2. (Cyclin D1 x400)	<b>92</b>
<b>15</b>	Prostatic adenocarcinoma pattern 3 with rounded and angulated glands showing strong nuclear Cyclin D1 staining, grade 3. (Cyclin D1 x100)	<b>93</b>
<b>16</b>	Prostatic adenocarcinoma pattern 3 with rounded and angulated glands showing strong nuclear Cyclin D1 staining, grade 3. (Cyclin D1 x200)	<b>93</b>
<b>17</b>	Strong nuclear Cyclin D1 staining (grade 3) in pattern 4 (signet cell ring feature) + negative nuclear staining (grade 0) in adjacent PIN. (Cyclin D1 x400)	<b>94</b>
<b>18</b>	Strong nuclear Cyclin D1 staining (grade 3) in both pattern 4 (cribriform pattern) & adjacent pattern 3 (rounded and angulated glands) prostatic adenocarcinoma.	<b>94</b>
<b>19</b>	Prostatic adenocarcinoma pattern 4 with fused acini showing strong nuclear Cyclin D1 staining (grade 3) + adjacent pattern 3 with rounded and angulated glands showing moderate nuclear Cyclin D1 staining (grade 2). A) (Cyclin D1 x200) & B) (Cyclin D1 x400)	<b>95</b>

## INTRODUCTION

Prostate cancer is a common and growing public health problem. The etiology of this cancer is not fully understood (***Rochester and Hellawel, 2004***). Prostate cancer occurs when cells of the prostate mutate and begin to grow out of control. Prognostic criteria currently in use cannot fully predict tumor behavior. The search for better prognostic markers is now focused on the molecular mechanisms such as altered cell cycle progression, apoptosis, neuroendocrine differentiation and angiogenesis, which underlay tumor behavior (***El sharkawy et al., 2009***).

Cyclin D<sub>1</sub>, a cell regulatory protein, considered a product of Cyclin D<sub>1</sub> protooncogene is an important regulator of G<sub>1</sub> to S-phase transition of the cell cycle. It is believed to play an important role in both tumorigenesis and grading of many cancers including prostatic carcinoma if its expression is deregulated, mainly over expressed (***He et al., 2007***).

Despite the influence of D-type Cyclins on prostate cancer proliferation, few studies have examined the expression of Cyclin D<sub>1</sub> in localized tumors or challenged its relevance to disease progression (***Comstok et al., 2007***).

Moreover the variation in the results of previous researches that studied the relationship between Cyclin D<sub>1</sub> and prostatic carcinoma was both variable and valuable. No correlation was found between Cyclin D<sub>1</sub> overexpression and either Gleason score, neoadjuvant hormone treatment or prostatic-specific antigen (***Drobnjak et al., 2000***). Overexpression of Cyclin D<sub>1</sub> rarely occurs in human prostate tumors and when it does it may identify a subset of tumor with a different molecular biology (***Gumbiner et al., 1999***). There was a relation-ship between Gleason grade and

staining for Cyclin D<sub>1</sub> (*Ozbek et al., 2000*). Cyclin D<sub>1</sub> expression levels are elevated in malignant human prostatic epithelial cell lines and its overexpression in benign prostatic hyperplasia cells can increase cell proliferation rate, migration and invasive ability (*He et al., 2007*).

The relevance of altered Cyclin D<sub>1</sub> status was observed; differential Cyclin D<sub>1</sub> status may influence clinico-pathological parameters and reveal new insight as to the regulation and potential consequence of Cyclin D<sub>1</sub> expression in prostate cancer. Tumors with predominantly cytoplasmic Cyclin D<sub>1</sub> showed the lowest ki-67 index, whereas nuclear Cyclin D<sub>1</sub> was associated with higher grade and elevated ki-67 (*Comstock et al., 2007*).

The increased expression of Cyclin D<sub>1</sub> in prostate cancer samples suggests that further studies on the expression of this gene may be of interest in understanding the pathogenesis of prostate cancer, moreover the positive correlation between Gleason grade and protein expression may be used as a prognostic marker in prostate cancer (*Ozbek et al., 2000*).

## AIM OF THE WORK

- To investigate immunohistochemical expression of Cyclin D<sub>1</sub> in prostatic carcinoma.
- To investigate the relationship between Cyclin D<sub>1</sub> expression and clinical data (e.g. age and serum PSA level), PIN, histopathological features and different Gleason grades and stages of prostatic carcinoma.
- To prove or disprove an association or relation between Cyclin D<sub>1</sub> expression and different Gleason grades and stages of prostatic carcinoma, thus allowing the use of Cyclin D<sub>1</sub> as a prognostic marker for prostatic carcinoma.

# ANATOMY AND HISTOLOGY OF THE PROSTATE

## **ANATOMY OF THE PROSTATE:**

The prostate has been variously described as looking like a walnut, a chestnut or a small palm. In a young man, it weighs approximately 20 grams then it increases in size as the man ages (*Torrey et al., 2008*). The normal adult prostate has average dimensions of 33mm in height, 24mm in thickness and 44mm in width. The base of the prostate refers to the cranial aspect of the gland, closer to the bladder. The apex of the prostate is the most caudal portion of the gland adjacent to the pelvic floor (*Halpern et al., 2002*). According to the classification of *Lowsely*, the prostate consists of five lobes: anterior, posterior, median, right lateral and left lateral (*Tanagho et al., 2004*).

### **Zones of the prostate:**

According to *McNeal (1972)* the prostate gland is divided into three zones (*Tanagho et al., 2004*). The prostate is divided into these zones by the urethra which is formed at the bladder neck and turns anteriorly 35° at its mid portion to exit the prostate at its apex (*Humphrey, 2003*).

#### **1) *The transition zone:***

The transition zone wraps around the prostatic urethra and makes up to 5% of the prostate gland volume (*Humphrey, 2003*). This region lies anterior to the central zone and medial to the peripheral zone. The

transition zone is the site of origin of most of hyperplastic nodules (*Petersen et al., 2008*).

**2) *The central zone:***

The central zone is a posteriorly situated cone shaped structure with its base projecting towards the bladder, making up to 25% of the prostate gland volume and having the two ejaculatory ducts passing through it from seminal vesicles to open at the posterior urethral protuberance known as the verumontanum (*Humphrey, 2003*).

**3) *The peripheral zone:***

The peripheral zone forms the bulk of the posterior, lateral and apical portions of the prostate gland accounts for 70% of the total gland volume (*Humphrey, 2003*). The peripheral zone is the zone which is susceptible to be affected by prostatitis and prostatic carcinoma (*Rosai and Ackerman, 2004*).

**Relations of the prostate:**

• *Anteriorly:*

The prostate is related to the symphysis pubis, separated from it by the extraperitoneal fat in the retropubic space (cave of Retzius). The prostate is connected to the posterior aspect of the pubic bones by the fascial puboprostatic ligament (*Snell, 2007*). Anterior to the prostate is the fascia of Zukerkondl which contains the venous plexus of Santorini (*Halpern et al., 2002*).