CYCLIN D_1 EXPRESSION IN PROSTATIC CARCINOMA

T H E S I S

Submitted for Fulfillment of the Master Degree (M.Sc.) in Pathology

By

Marwa Abd El-Rahman Mohamed Abd El -Rahman El Borady

(M.B.B.Ch.), Faculty of Medicine,
Cairo University

Under Supervision of

Prof. Dr. Elia Anis Ishak

Professor of Pathology
Faculty of Medicine
Cairo University

Prof. Dr. Menar Mohamed Ayoub

Professor of Pathology
Faculty of Medicine
Cairo University

Dr. Hala Mahmoud Naguib Hosni

Lecturer of Pathology
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2009

ACKNOWLEDGMENT

First and foremost **"Thanks to GOD"**, the most merciful and kind.

I am very much indebted to **Prof. Dr. Elia Anis Isak,** *Professor of Pathology, Faculty of medicine, Cairo University, I would like to express my deepest gratitude, great thanks, and appreciation to him for his close supervision, precious remarks and great experience and effort that were very valuable both in selecting the subject and completing this work.*

I am very grateful to **Prof. Dr. Menar Mohamed Ayoub,** *Professor of Pathology, Faculty of medicine, Cairo University for her precious remarks, kind guidance and valuable advices that encouraged and helped me so much.*

I would like to sincerely thank **Dr. Hala Naguib Hosny,** *Lecturer of Pathology, Faculty of Medicine, Cairo University who saved no time and effort in helping me, her constant support, continuous encouragement and constructive criticism allowed me to accomplish this work.*

I am deeply thankful to **Dr. Hoda Ibrahim Ibrahim,** *Assistant Lecturer of Community Medicine, Faculty of medicine, Cairo University, for performing the statistics of this work and for the precious time she offered to help me.*

Finally I would like to thank my precious and kind family, without their love, motivation, support and encouragement, this work would have never seen light.

Marwa Abd El Rahman

ABSTRACT

Prostatic carcinoma is a common and growing public health problem. Cyclin Dı is a cell regulatory protein, which is believed to play an important role in both tumorgenesis and grading of many cancers. The role of Cyclin D1 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_1 was evaluated in all cases. Correlation between the intensity of Cyclin D1 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 D1 with different grades of intensity ranging from moderate to strong, while positive Cyclin D1 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 D1 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 D1 and preoperative serum PSA level was observed

Cyclin D1 expression might affect PSA expression, which is considered an important tumor marker. Cyclin D1 plays an important role in the pathogenesis and evolution of prostate cancer rather than the prognosis, thus Cyclin D 1 is not a reliable prognostic factor in cancer prostate.

Key words: Cyclin D1-Prostatic carcinoma.

CONTENTS

LIST OF ABBREVIATION

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

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

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 D1, a cell regulatory protein, considered a product of Cyclin D1 protoncogene is an important regulator of G1 to S-phase transition of the cell cycle. It is believed to play an important role in both tumorgenesis 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 D1 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 D1 and prostatic carcinoma was both variable and valuable. No correlation was found between Cyclin D1 overexpression and either Gleason score, neoadjuvat hormone treatment or prostatic-specific antigen ***(Drobnjak et al., 2000).*** Overexpression of Cyclin D1 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 D1 ***(Ozbek et al., 2000).*** Cyclin D1 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 D1 status was observed; differential Cyclin D1 status may influence clinico-pathological parameters and reveal new insight as to the regulation and potential consequence of Cyclin D1 expression in prostate cancer. Tumors with predominantly cytoplasmic Cyclin D1 showed the lowest ki-67 index, whereas nuclear Cyclin D1 was associated with higher grade and elevated ki-67 ***(Comstock et al., 2007).***

The increased expression of Cyclin D1 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 el al., 2000).***

AIM OF THE WORK

- To investigate immunohistochemical expression of Cyclin D_1 in prostatic carcinoma.
- To investigate the relationship between Cyclin D_1 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_1 expression and different Gleason grades and stages of prostatic carcinoma, thus allowing the use of Cyclin D_1 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 35º 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 symphisis 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).***