Evaluation of β-Catenin in Bladder Transitional Cell Carcinoma

Thesis

Submitted for partial fulfillment of M.D Degree in Urology

By

Hatem Zaki El Wardany

M.B., B.Ch. – M.Sc.

Supervised By

Prof. Dr. Tarek Mostafa El Zayat

Professor of Urology

Faculty of Medicine - Ain Shams University

Dr. Mohamed Ibrahim Shaban

Assistant Professor of Pathology

Faculty of Medicine Menoufiya University

Dr. Ahmed Ibrahim Radwan

Lecturer of Urology

Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University

2018

قَالُوا سُبْحَانَكَ لا عِلْمَ لَنا إِلَّا ما عَلَّمْتَنا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة (٣٢)

Acknowledgement

First and above all, thanks and gratitude to the ***Merciful ALLAH*** *for helping me complete this work.*

It is my pleasure to express my sincere gratitude to ***Prof. Dr. Tarek Mostafa EL-Zayat*** *Professor of Urology, Faculty of Medicine, Ain Shams University who put the idea for this thesis. It was a great honor to me to do this work* under *his supervision. He will remain a model of wisdom to me.*

I am much grateful for ***Dr. Mohammad Ibrahim Shabban,*** *Assistant Prof. of Pathology, Faculty of medicine, Menoufiya University, for his experienced guidance and helpful suggestions that made the completion of this work possible.*

My deep thanks to ***Dr. Ahmed Ibrahim Radwan****, Lecturer of Urology, Faculty of Medicine, Ain Shams University, for his continuous help, valuable discussion, advice and criticism and continuous guidance, also incredible working capacity for writing this thesis.*

Thanks to ***Mr. Mohamed EL-Shafey****, Pathology Technician, Pathology department, Faculty of Medicine, Menoufiya University for his sincere hard working & help finishing the laboratory work of this thesis.*

Last, but not least, I would like to thank my family for their actual help and support received in many ways.

Hatem EL-Wardany

List of Contents

List of abbreviation

%	Percentage
µm	Micrometer
4p16.3	Short arm of chromosome 4 region 1 band 6 sub band 3
AJs	Adherens junctions
APC	Adenomatus polyposis coli gene
AUS	Atypia with unknown significance
BCL2	B-Cell CLL/Lymphoma 2
BCRC	Bladder Cancer Research Consortium
BSA	Buffer and sodium Azide
c.c.	Cubic centimeter
CA-125	Carbohydrate antigen 125
CBC	Complete blood count
CBS	Citrate buffer solution
CD	Cluster of differentiation
CEA	Carcinoembrionic antigen
c-erbB-2	HER2/neu, human EGF receptor 2, and human epidermal growth factor receptor 2.
CI	Confidence interval
CIS	Carcinoma in situ
CK 20	Cytokeratin 20
c-Myc	Myelocytomatosis
CRC	Colorectal cancer
CT	Computerize tomography
C-terminus	Carboxyl terminus
DAB	Diaminobenzidine tetrahydrochloride
ddH2O	Double distilled water
DRE	Digital rectal examination
EGF	Epidermal growth factor
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	European Prospective Investigation into Cancer and Nutrition

F.E	Fisher's exact test
FAP	Familial adenomatous polyposis coli
FGFR3	Fibroblast growth factor receptor 3
Fz	Frizzled
GR	Grade of Recommendation
GSK3β	Glycogen synthase kinase
GSTM1	Glutathione S-Transferase M1
GTPases	Guanosine triphosphate hydrolase
H. & E.	Hematoxylin & Eosin
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
Hcl	Hydrochloric acid
HER-2	Human EGF (Epidermal Growth Factor) Receptor 2
HIER	Heat induced epitope retrieval
HPV	Human papillomavirus
HR	Hazard ratio
IgG	Immunoglobulin G
IP	Inverted papilloma
IRS	Immunoreactive score
ISUP	International Society of Urological Pathology
IVU	Intravenous Urography
K2HPO4	Dipotassium hydrogen phosphate dibasic
kDa	Kilo Dalton
KH2 PO4	Potassium Dihydrogen Orthphosphate
KI-67	Antigen KI-67
KUB	Kidney Ureter bladder
LE	Level of Evidence
LEF	Lymphoid enhancer factor
LOH	Loss of heterozygosity
LRR	Leucine-rich repeats
MDB	Medulloblastoma
mesna	Mercaptoethane sulfonate Na

MIBC	Muscle Invasive Bladder Cancer
mm	Millimeter
MMTV	Mouse mammary tumour virus
MRI	Magnetic resonance imaging
MUC5AC	Mucin-5AC protein
M-VAC	Methotrexate , Vinblastine , Doxorubicin which was originally called Adriamycin®, Cisplatin
MVD	Micro-vessel density
Nacl	Sodium chloride
NaOH	Sodium hydroxide
NAT	N-acetyl transferase
HGPUC	High-grade papillary urothelial carcinoma
LGPUC	Low-grade papillary urothelial carcinoma
NMIBC	Non Muscle Invasive Bladder Cancer
P21	Myclin-dependent kinase inhibitor 1 or CDK-interacting protein 1
P27	Cyclin-dependent kinase inhibitor 1B (p27Kip1)
PBS	Phosphate buffered saline
PH	Inverted log of hydrogen ion concentration
PIK3CA	Phosphatidyl-inositol-3-kinase CA
PSA	Prostate-specific antigen
PSCA	Prostate stem cell antigen gene
PTR	Pilomatrixoma
PUNLMP	Papillary Urothelial Neoplasia of Low Malignant Potential
RA	Reactive atypia
Rb	Retinoblastoma gene
RC	Radical cystectomy
RNA	Ribonucleic Acid
ROK	Rho kinase
SEER	Surveillance Epidemiology and End Results
SFRP	Secreted frizzled receptor proteins
SNP	Single neucleotide polymorphism
SPSS	Statistical Package for the Social Sciences

SD	Standard deviation
TCC	Transitional cell carcinoma
TCF	T-cell factor
TILs	Tumor infiltrating lymphocytes
TNM	Tumor, nodes, and metastases
Tp53	Tumor Protein 53
TUR	Trans urethral resection
TURBT	Transurethral resection of bladder tumor
BC	Bladder Carcinoma
EBRT	External-beam radiotherapy
RP	Radical prostatectomy
BT	Brachytherapy
IMRT	Intensity-modulated radiotherapy
PDD	Photodynamic diagnosis
ALA	Aminolaevulinic acid
HAL	Hexaminolaevulinic acid
BCG	Bacillus Calmette-Guerin
DCE	Dynamic contrast-enhanced
NSF	Nephrogenic systemic fibrosis
PET	Poitron emission tomography
NAC	Neoadjuvant chemotherapy
OS	Over all servival
RCT	Randomised controled trial
CRs	Complete remissions
SI	Single instillation
SCC	Squamous cell carcinoma
UTI	Urinary tract infection
LUTS	Lower urinary tract symptoms
UTUC	Upper tract urothelial carcinoma
US	Ultrasound
BTA	Bladder Tumour Antigen
GWAS	Genome-wide association studies

UD	Urothelial Dysplasia
UH	Urothelial hyperplasia
UP	Urothelial papilloma
VEGF	Vascular endothelial growth factor
VHL	Von Hippal Lindal
wg	Gene wingless
WHO	World health organization
Wnt	Wingless Pathway
X^2	Chi- square
yr	Year
β	Beta

List of tables

List of Figures

Introduction

Bladder cancer is the fourth most common cancer occurring in United States, second most prevalent cancer in men and tenth most prevalent cancer in women, with age adjusted incidence rate of 24.5 per 100.000 population and mortality rate of 4.2 per 100.000 population per year **(Pashos et al., 2002).** Because of its high recurrence rate, the actual prevalence of active bladder cancer is estimated to be about 10 times the number of new cases **(Stein et al., 2001)**.

Bladder cancer is still the most frequent malignant tumor among Egyptian males, currently; it ranks first in males, representing 16.2% of male cancers. Among Egyptian females, its frequency is 4%. For both sexes together, the frequency of bladder cancer is 10.1% **(Khaled, 2005).**

Bladder cancer is a heterogeneous disease with a variable natural history. Approximately 70–80% of patients present with noninvasive (pTa) or superficially invasive (pT1) tumors at the time of initial diagnosis; the remaining 20–30% initially present with muscle-

invasive tumors (pT2–4) **(Van Rhijn et al., 2009; Bostrom et al., 2010).**

Muscle-invasive bladder cancer treatment requires a radical cystectomy or chemotherapy with radiation protocol. Radical cystectomy has many quality of life implications. In addition, the absolute survival benefit of neoadjuvant or adjuvant chemotherapy is debatable, and toxicity can be significant. Despite the current treatments, distant metastases eventually may develop in as many as 50% of patients with muscle-invasive tumor. Treatment options for metastatic bladder cancers are extremely limited, with a 5-year survival rate of 6% and a median survival time of 12 to 20 months. Therefore, it is generally believed that there is an urgent need to expand the current paradigm of therapy by integrating novel targeted therapies for muscle-invasive bladder cancer **(Snyder et al., 2003).**

The wingless-type (Wnt) pathway plays a central role in embryonic development. Aberrant activation of the Wnt pathway contributes to the progression of several major human cancers. Therefore, inhibition of Wnt effects has major therapeutic potential **(Tang et al., 2009).**