

# **Evaluation of $\beta$ -Catenin in Bladder Transitional Cell Carcinoma**

*Thesis*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

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# List of Contents

Title	
List of abbreviation	I
List of Tables	II
List of Figures	VIII
Introduction	1
Aim of the work	4
Review of literature	5
• Bladder cancer	5
• Histopathology of bladder cancer	15
• Diagnosis of bladder cancer	39
• $\beta$ -catenin	55
Patients and methods	66
Results	82
• Demographic data	83
• Histopathological data	86
• Immunohistochemical data of $\beta$ -catenin:	90
Discussion	109
Summary	118
Conclusions	124
Recommendations	125
References	126

## List of abbreviation

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

<b>F.E</b>	Fisher's exact test
<b>FAP</b>	Familial adenomatous polyposis coli
<b>FGFR3</b>	Fibroblast growth factor receptor 3
<b>Fz</b>	Frizzled
<b>GR</b>	Grade of Recommendation
<b>GSK3<math>\beta</math></b>	Glycogen synthase kinase
<b>GSTM1</b>	Glutathione S-Transferase M1
<b>GTPases</b>	Guanosine triphosphate hydrolase
<b>H. &amp; E.</b>	Hematoxylin & Eosin
<b>HCC</b>	Hepatocellular carcinoma
<b>HCG</b>	Human chorionic gonadotropin
<b>Hcl</b>	Hydrochloric acid
<b>HER-2</b>	Human EGF (Epidermal Growth Factor) Receptor 2
<b>HIER</b>	Heat induced epitope retrieval
<b>HPV</b>	Human papillomavirus
<b>HR</b>	Hazard ratio
<b>IgG</b>	Immunoglobulin G
<b>IP</b>	Inverted papilloma
<b>IRS</b>	Immunoreactive score
<b>ISUP</b>	International Society of Urological Pathology
<b>IVU</b>	Intravenous Urography
<b>K2HPO4</b>	Dipotassium hydrogen phosphate dibasic
<b>kDa</b>	Kilo Dalton
<b>KH2 PO4</b>	Potassium Dihydrogen Orthphosphate
<b>KI-67</b>	Antigen KI-67
<b>KUB</b>	Kidney Ureter bladder
<b>LE</b>	Level of Evidence
<b>LEF</b>	Lymphoid enhancer factor
<b>LOH</b>	Loss of heterozygosity
<b>LRR</b>	Leucine-rich repeats
<b>MDB</b>	Medulloblastoma
<b>mesna</b>	Mercaptoethane sulfonate Na

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

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

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

### List of tables

Table No.	Title	Page No.
(1)	Histologic Characteristics of Noninvasive Papillary Urothelial Tumors of the Bladder According to the World Health Organization 2004 Classification	18
(2)	Histologic Type of Tumors of the Urinary Bladder According to the World Health Organization 2004 Classification	19
(3)	Clinical Significance of Different Non-Muscle-Invasive Urothelial Cancer Categories in the World Health Organization 2004 Grading System	21
(4)	Definition of TNM	26
(5)	Urinary molecular marker tests	42
(6)	Summary of evidence and specific recommendations for the primary assessment of presumably invasive bladder tumours	50
(7)	proteins believed to be involved regulation of $\beta$ -catenin	62
(8)	Demographic data of the studied control group	83
(9)	Demographic data of the studied UBC cases	83
(10)	Histopathological data of the studied UBC cases	86
(11)	Correlation between $\beta$ -catenin expression in the control group versus the UBC group	91
(12)	Catenin positivity in UBC cases and its relation to the studied clinical parameters	93
(13)	Catenin positivity in UBC cases and its correlation to the studied histopathological parameters	94
(14)	Correlation between cellular <i>localization</i> of $\beta$ -catenin positivity in UBC cases and the various clinical parameters	96
(15)	Subcellular localization of $\beta$ -catenin in positive UBC cases and its	98

Table No.	Title	Page No.
	correlation to the studied histopathological parameters	
<b>(16)</b>	Correlation between intensity of $\beta$ -catenin expression in UBC cases and various clinical parameters	<b>102</b>
<b>(17)</b>	Score of $\beta$ -catenin in positive UBC cases and its relation to the studied clinical parameters	<b>104</b>

## List of Figures

Figures No.	Title	Page No.
(1)	Normal urothelium.	15
(2)	Carcinoma in situ.	22
(3)	low-grade papillary urothelial neoplasm	24
(4)	High grade papillary urothelial neoplasm	25
(5)	Nested Variant of Urothelial Carcinoma	34
(6)	Clear cell adenocarcinoma of the bladder. Infiltrating adenocarcinoma, showing acini, nests, and infiltrating single cells composed predominantly of cells with clear cytoplasm.	35
(7)	Adenocarcinoma of the bladder. Transurethral resection of the prostate fragment showing extensive involvement by primary bladder adenocarcinoma. Note presence of cribriform and glandular architecture of tumor (inset)	37
(8)	Wnt ligands at the cell surface activate at least 5 different pathways. The best characterised is the 'canonical' $\beta$ - catenin/TCF pathway	58
(9)	The Wnt/ $\beta$ -catenin signaling pathway.	61
(10)	Acute of cystitis showed normal transitional epithelial covering with fibrosis and chronic inflammatory cells in the sub epithelial tissue	85
(11)	histopathological data of the studied UBC case frequencies.	87
(12)	Acute of transitional cell carcinoma low grade showed sheets and cords of malignant epithelial cells invading the submucosa and revealed mild to moderate degree of anaplasia	88
(13)	Acute of transitional cell carcinoma high grade showed sheets and cords of malignant epithelial cells invading the submucosa and revealed high degree of anaplasia.	88
(14)	Acute of papillary transitional cell carcinoma low grade showed sheets and papillary fronds formed of fibrovascular	89

	core covered by malignant urothelial revealed mild degree of anaplasia	
<b>15</b>	Correlation between catenin expression in the control group versus UBC group.	<b>92</b>
<b>16</b>	catenin expression in UBC cases and its correlation to the studied histopathological parameters	<b>95</b>
<b>17</b>	Correlation between cellular localization of catenin in UBC cases and the various clinical parameters	<b>97</b>
<b>18</b>	subcellular localization catenin in positive UBC cases and its correlation to the studied histopathological parameters.	<b>100</b>
<b>19</b>	correlation between intensity of catenin expression in UBC case and various clinical parameters	<b>103</b>
<b>20</b>	score of catenin in positive UBC cases and its relation to the studied clinical data	<b>105</b>
<b>(21)</b>	A case of low grade transitional cell carcinoma showed mild positivity of B-catenin in tumour cells (IHCx100).	<b>106</b>
<b>(22)</b>	A case of low grade transitional cell carcinoma showed moderate positivity of B-catenin in tumour cells (IHCx100)	<b>106</b>
<b>(23)</b>	A case of high grade transitional cell carcinoma showed strong positivity of B-catenin in tumour cells (IHCx200).	<b>107</b>
<b>(24)</b>	A case of papillary transitional cell carcinoma showed moderate positivity of B-catenin in tumour cells (IHCx200).	<b>107</b>
<b>(25)</b>	A case of cystitis (control group) showed negative expression of B-catenin in urothelial cells (IHCx200).	<b>108</b>

## **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**).