INTRODUCTION

Urinary bladder cancer is ranked as ninth in cancer incidence worldwide ***(Parkin et al., 2008).***

In Egypt, urinary bladder carcinoma is the most prevalent cancer, accounting for 31% of all cancer cases ***(WHO Expert Committee, 1993)*** and currently, it ranks first in males accounting for 16.2% of male cancer ***(Khaled et al., 2005).***

At the time of diagnosis, urothelial tumors can be classified histopathologically into 2 groups: non-muscle invasive papillary tumors "Ta & T1" (80% of bladder tumors) and muscle invasive tumors (the remaining 20%) ***(Rodriguez et al., 2000).***

Standard treatment for muscle-invasive urothelial carcinomas is cystectomy, and by transurethral resection (TUR) for superficial tumors. But patients with superficial urothelial carcinomas have a high risk of recurrence even after initial complete TUR (approximately 30% to 80%) Also 1% to 45% of these carcinomas progress to muscle-invasive disease ***(Kaufman et al., 2009 & Burger et al., 2009).***

Many prognostic parameters related to tumor recurrence and progression have been investigated; however, no reliable parameters have been identified for predicting the risk of recurrence or progression. The initiation and progression of

urinary bladder carcinoma involve a sequence of genetic events, including the activation of oncogenes and inactivation of tumor suppressor genes ***(Karam et al., 2008 & Yang et al., 2009).***

The ETS-1 protooncogene is a transcription factor that has a role in extracellular matrix (ECM) remodeling. It regulates various physiological processes, such as embryogenesis, wound healing, and pathological processes, such as tumor progression by activating the transcription of some proteases including matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator ***(Saeki et al., 2000 & Nakayama et al., 2001).***

These proteases account for ECM degradation, which is a key event in invasion ***(Dittmer et al., 2003).***

ETS-1 also activates MMPs in endothelial cells ***(Keehn et al., 2004)*** resulting in endothelial cell proliferation and activation, which in turn results in angiogenesis ***(Keehn et al., 2003).***

Elevated ETS-1 expression has been documented in the carcinogenesis, invasion and progression of different solid tumors, such as stomach cancer ***(Nakayama et al., 1996 & Zhang et al., 2003),*** colon cancer ***(Nakayama et al., 2001)***, lung cancer ***(Takanami et al., 2001 & Nakayama et al., 2007)*** and oral squamous cell carcinomas ***(Pande et al., 1999).***

An inverse relationship was found between ETS-1 expression and differentiation of other tumors. ETS-1 expression was lower in moderately & poorly differentiated HCCs than in well differentiated HCC ***(Ito et al., 2000)***. In thyroid carcinomas, its expression was lower in anaplastic carcinoma than in follicular or papillary carcinoma ***(Nakayama et al., 1999).***

AIM OF THE WORK

The present study aims at evaluating the significance of ETS-1 expression in urothelial (transitional cell) carcinoma of the urinary bladder & determining the relationship of this oncoprotein with the histopathological parameters including tumor grade and stage.

ANATOMY & HISTOLOGY OF THE URINARY BLADDER (UB)

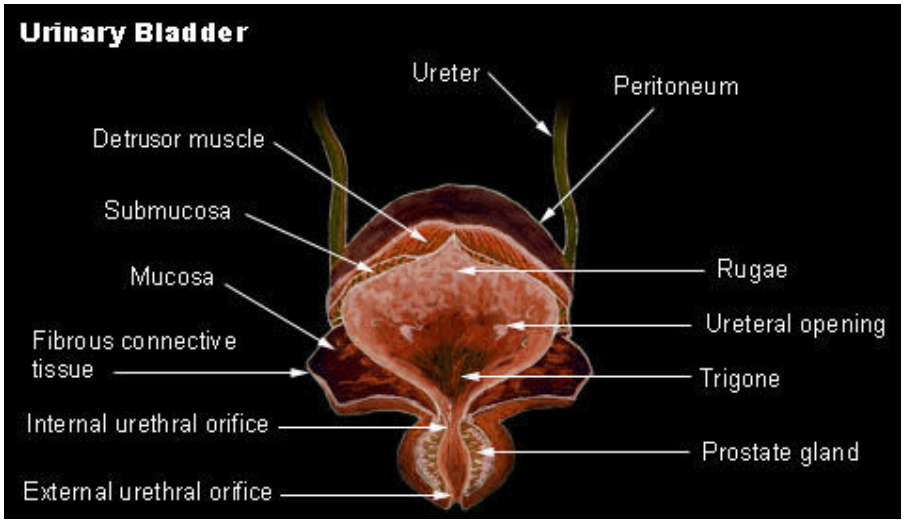

Fig. (1): Anatomy of the Urinary Bladder
(http://www.histology-world.com)

The urinary bladder is a expandable musculo-membranous hollow sac which lies within the pelvic cavity behind the symphysis pubis (Fig. 1)

It contains three openings, two for the ureters (ureteric orifices) and one for the urethra (internal urethral orifice). The triangular region defined by these three openings, the trigone, is relatively smooth and constant in thickness, whereas the rest of the bladder wall is thick and folded when the bladder is empty and thin and smooth when the bladder is distended ***(Henry Gray, 1918).***

The orifices of the ureters are placed at the postero-lateral angles of the trigone, and are usually slit-like in shape.

The internal urethral orifice is placed at the apex of the trigone, in the most dependent part of the bladder, and is usually somewhat crescentic in form ***(Henry Gray, 1918).***

Blood Supply and Innervation:

The arteries supplying the bladder are the superior, middle, and inferior vesical, derived from the anterior trunk of the hypogastric. The obturator and inferior gluteal arteries also supply small visceral branches to the bladder, and in the female additional branches are derived from the uterine and vaginal arteries.

The veins form a complicated plexus on the inferior surface, and fundus near the prostate, and end in the hypogastric veins.

The nerves of the bladder are fine medullated fibers from the third and fourth sacral nerves, and non-medullated fibers from the hypogastric plexus. They are connected with ganglia in the outer and submucous coats and are finally distributed, all as non-medullated fibers, to the muscular layer and epithelial lining of the viscus ***(Henry Gray, 1918).***

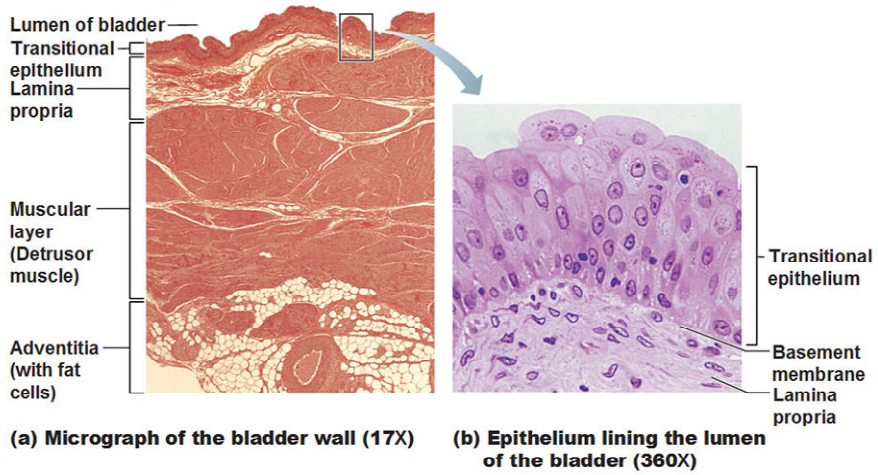

Fig. (2): Histology of the UB ***(http://antranik.org/the-urinary-system-ureter-and-urinary-bladder/)***

The wall of the urinary bladder is composed of the following layers: (Fig. 2)

1- The Mucosa:

The innermost portion of the urinary bladder which is composed of transitional epithelium (urothelium) and connective tissue.

The thickness of the urothelium varies accoding to the degree of distension of the bladder. In the empty bladder the epithelium can be up to seven cells thick. The deepest (basal) cells have a cuboidal or columnar shape above which are several layers of irregular polyhedral cells. The most superficial (luminal or apical) layer consists of large, sometimes binucleated eosinophilic dome-shaped cells with abundant cytoplasm and a rounded free surface called superficial, apical or umbrella cells ***(Bloom et al., 1986) (Fig. 3).***

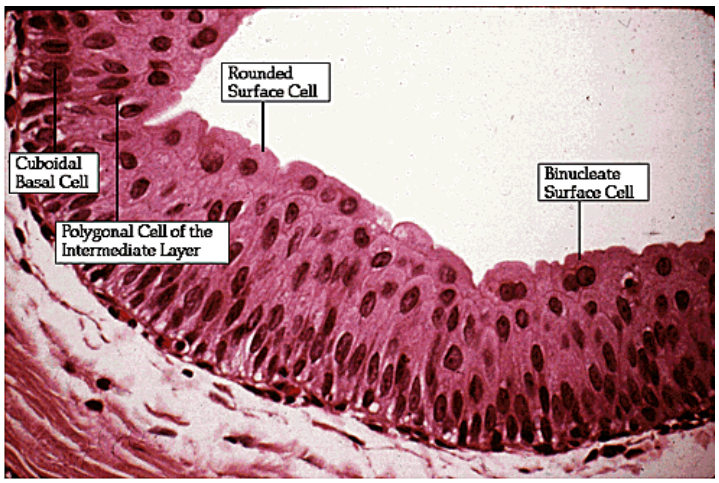

Fig. (3): Layers of the transitional epithelium
(http://education.med.nyu.edu/Histology/)

In the distended bladder, the epithelial lining can be as few as two cells thick, with a basal layer of cuboidal cells and a superficial layer of elongated & flattened cells, umbrella cells are inconspicuous (Fig. 4).

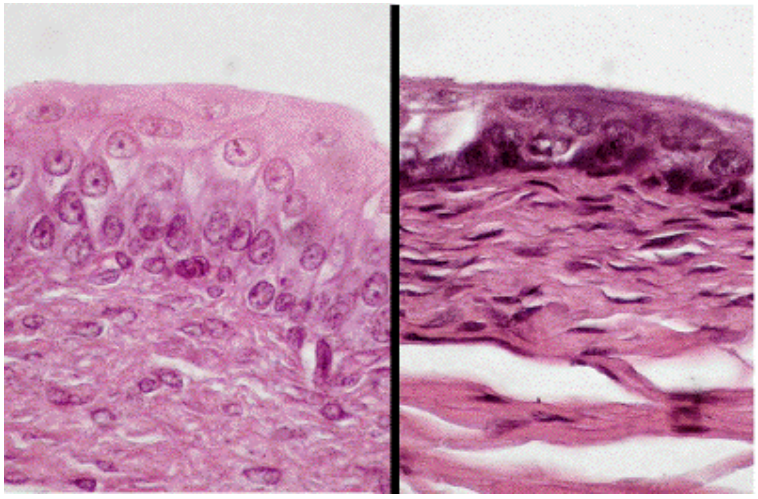

Fig. (4): Transitional epithelium in collapsed (left) and distended (right) bladders ***(http://www.dartmouth.edu/).***

The epithelial layer contains no blood vessels or lymphatics ***(Ross et al., 2003).***

The basement membrane separates the urothelium from the underlying lamina propria ***(Ross et al., 2003).*** The latter is formed of abundant areolar connective tissue which contains a rich vascular network lymphatic channels, sensory nerve endings, and few elastic fibers. The lamina propria varies in thickness in the empty versus the distended bladder, but is generally thinner in the areas of the trigone and bladder neck. Wisps of smooth muscle may be found within the superficial lamina propria, either isolate or forming a complete or incomplete muscularis mucosa ***(Elnaggar et al., 1987 & Reuter et al., 1996).***

2- The Muscularis Propria:

Underneath the mucosa of the bladder is a layer called the muscularis propria. The muscularis is smooth muscle which is subdivided into three layers: inner longitudinal, middle circular, and outer longitudinal ***(Ross et al., 2003).***

The internal & external longitudinal layers are lossely anastomosing & ill-defined. The middle circular layer is more prominent. In the bladder neck of the male, the fascicles of the muscularis propria are continuous with the fibromuscular tissue of the prostate, while in the female, they are continuous with the muscle fibers in the wall of the urethera ***(Bloom et al., 1986).***

The smooth muscle of the bladder is called the detrusor muscle & its contraction expels urine from the bladder ***(Ross et al., 2003).***

Fat can be encountered within the muscularis propria ***(Amin et al., 2000).***

3- The Serosa/Adventita:

The outermost layer of the bladder is adventita which is composed of connective tissue except the superior surface which is covered by the serosa, a reflection of the pelvic peritoneum & composed of a simple squamous epithelium overlying a small bit of connective tissue. Beyond the serosa/adventitia covering of the bladder is perivesical fat. This is a layer of fat surrounding bladder ***(Ross et al., 2003).***

EPIDEMIOLOGY OF UB CANCER

Urinary bladder cancer (UBC) is a common disease worldwide. The incidence of UBC varies over the world with highest rates in developed communities. But the burden of UBC will increase in less developed areas of the world. These changes can be attributed to global changes in exposure to risk factors for UBC and growth and aging of the world population ***(Ploeg et al., 2009).***

Urinary bladder cancer ranks ninth in worldwide cancer incidence. It is the seventh most common malignancy in men and seventeenth in women ***(Ploeg et al., 2009).*** An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide ***(Jemal et al., 2011).***

In the Western world, bladder cancer is the fourth most common malignancy in men and the eighth most common in women. In Europe and the United States, bladder cancer accounts for 5% to 10% of all malignancies in men. The risk of developing bladder cancer at <75 years of age is 2% to 4% for men and 0.5% to 1% in women ***(Ziya et al., 2005).***

The majority of bladder cancer occurs in males. The highest incidence rates are found in the countries of Europe, North America, and Northern Africa ***(Ferlay et al., 2008).***

Bladder cancer incidence and mortality show a decrease in Western communities over the last decades ***(Karim-Kos et al., 2008)*** found a decline in UBC occurrence in most countries

of Europe (with the exception of Central Europe) since mid 1990. In the US declining trends in incidence were seen between 1987 and 2005 ***(Ries et al., 2008).***

BC is diagnosed almost twice as often in whites as in blacks of either sex. The incidence of bladder cancer among other ethnic and racial groups in the United States falls between that of blacks and whites ***(Wong et al., 2006).***

BC is a disease of older patients, most cases being older than 65 years but is not restricted to these groups. 3.1% of the new cases occurs in patients under the age of 44 years and 8% occurs in patients aged 45–54 years. Both the incidence and mortality increase with advancing age ***(SEER Program, 2004)***. People over the age of 70 develop the disease 2 to 3 times more often than those aged 55–69 and 15 to 20 times more often than those aged 30–54 ***(ACS, 2008).*** After the age of 80 years bladder cancer is twice as likely to develop and cause death as in those aged 60–65 years ***(SEER Program, 2004).***

Urinary Bladder Cancer in Egypt:

BC is one of the most common cancers in the Middle East countries. BC is the most prevalent cancer in most African countries.

During the past 50 years, BC has been the most common cancer in Egypt ***(Ploeg et al., 2009).*** Egypt has both higher frequency and incidence rates than other countries ***(Ibrahim and Khaled, 2006).*** In 2002, Egypt's world-standardized

bladder cancer revealed that Egypt has the highest incidence of BC in the world with an incidence of 37.1 per 100,000 representing approximately 30,000 new cases each year ***(Parkin et al., 2005 & Zaghloul et al., 2008).***

Egyptian males are almost two folds affected higher than in Western countries ***(Ploeg et al., 2009).*** Also, Egyptian males have the higher mortality rates (16.3 per 100,000), which is twice as high as the highest rates in Europe (8.3 in Spain and 8.0 in Poland) and over 4 times higher than that in the United States (3.7) ***(Jemal et al.,2011).***

BC constitutes 26.39% of all cancers, where it is the most common malignancy in men and the second most common malignancy in women after breast cancer according to the National Cancer Institute Cancer Pathology Registry between (1985-1989) ***(El-Mawla et al., 2001).*** While in the latter years of 2001 to 2005, this percentage declined significantly to account for approximately 12.2% of all cancers seen at the NCI-Cairo. Despite the significant decline in the relative frequency of bladder cancer in Egypt, a persistent gender disparity with predominance of the disease among males was observed. This gender gap might be a reflection of differences in the magnitude of environmental or lifestyle exposures related to bladder cancer etiology, such as schistosomal infection, smoking, and exposure to occupational and agriculture related chemicals ***(Felix et al., 2008).*** This gender-based trend might be due to a possible role of a tumor-

suppressor gene on the Y chromosome that has been deleted. Loss of the Y chromosome was observed in 7 of the 17 (41%) Schistosomiasis-associated bladder cancer cases studied by ***Khaled et al. (2000)*** using the fluorescence in situ hybridization (FISH) technique. Also, male predominance could be attributed to the fact that smoking rates and occupational exposures are more prevalent among males ***(Brennan et al., 2000 and 2001).***

Urinary bladder cancer accounted for 9.5% of all malignancies according to the population-based Gharbiah Governorate Cancer Registry 1999-2001 ***(Freedman et al., 2006)***. While, the Hospital Based Cancer Registry data at Ain Shams University Hospital and Ain Shams Specialized Hospital in the period from 2001-2005; showed that the relative frequency of urinary bladder malignancy cases received was 323 cases representing 5.1% of all malignancies ***(Mahmoud et al., 2009).***

The differences among these registries can be attributed to the nature of the material collected, geographical differences and the followed protocols of management ***(Mokhtar et al., 2007).***

In contrast to Western countries, more than two-thirds of bladder cancers in Egypt are squamous cell carcinoma (SCC) between 1960 and 1980, with a peak incidence at around 50 years of age, constituting from 59% to 81% of reported bladder cancers ***(El-Mawla et al., 2001)***. But the histopathological profile of bladder cancer in Egypt has changed significantly

over the past 26 years. Now transitional cell carcinoma (TCC) has become the most frequent type ***(Felix et al., 2008).*** The frequency of TCC in cystectomy specimens increased in the National Cancer Institute (NCI) from 30.5% in the period 1988-1991 to 44.1% in the period 1998–2001 ***(Zaghloul, 2008).***

Declining SCC rates and rising TCC rates suggest possible changes in the epidemiology of this disease in Egypt. Accordingly, bladder cancer cases recorded from 1980 through 2005 at the National Cancer Institute, Cairo were analyzed to evaluate temporal changes in histopathological types of cancers, and to assess associated changes in demographic, epidemiologic (changes in the risk factor profile related to bladder cancer) and lifestyle risk factors ***(Felix et al., 2008).***