TEN YEARS REVIEW OF **CANCER BLADDER** IN HOSPITAL UNIVERSITI SAINS MALAYSIA, KUBANG KERIAN

By

Dr.Ahmed Ali Abdullah Almotawakel
MBBS Sana'a

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (SURGERY)

Universiti Sains Malaysia
2006

III. ABSTRACT

The bladder constitutes the most frequent localization of malignant tumours in the urinary tract and it is one of the common urological malignancies occurring worldwide in both sexes. Local literature on bladder cancer are rather scare and hence the need for a study of this nature.

Sixty-seven patients with cancer of the bladder treated in a period of ten years from 1996 to 2005 at Hospital Universiti Sains Malaysia were studied to determine the pattern of the disease and highlight the clinical presentation, cystoscopic finding, histopathology and modalities offered for treatment of the disease.

It was found that the mean age of occurrence was 64.5 years. Male to female ratio was 5.7: 1 and predominantly affecting the Malays (86.57%). Sixty-one percent smoker with significant statistical correlation to tumour grade. The most common clinical presentations were haematuria (85.1%). Transitional cell carcinoma was found in 95.5% of studied population and most patients present with invasive stage (64.2%). TUR was done for 83.6% of them while 28.4% of patients underwent systemic chemotherapy therapy and 4.5% underwent radiotherapy.

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VII. ABBREVIATIONS.

BCG	Bacille Calmette-Guerin
CIS	carcinoma in-situ
cm	Centimeter
CT	Computed Tomography
DXT	Radiotherapy
G1,2,3	Grade 1, 2, 3.
HUSM	Hospital Universiti Sains Malaysia
IVU	Intravenous Uorogram
G1,2,3	Grade 1, 2, 3.
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
OT	Operation theater
RPG	Retrograde pyelogram
SCC	Squamous Cell Carcinoma
TCC	Transitional Cell Carcinoma
TUR	Transurethral resection
TURBT	Transurethral resection of bladder tumour
USA	United State of America
US	Ultrasound

VIII. ACKNOWLEDGMENT

I would like to express my special thanks and appreciation to Dr. Mohd Nor bin Gohar Rahman , Head of surgical department and the consultant urologist in Hospital Universiti Sains Malaysia , who suggest the topic of this study and was my supervisor and constantly guide me with great support toward the completion of the study.

Special thanks to Dr.Sarimah Abdullah, kamarul Imran Musa and Dr.Than Winn from community department school of medical science in Universiti sains Malaysia, who helped me in the epidemiological and statistical aspect of this study.

I also wish to thank Mrs. Zaini Mohd Noor and all the team of record office in Hospital Universiti Sains Malaysia for their great cooperation and assistance to provide me with patient's medical records and the required patients data.

1. INTRODUCTION

Bladder carcinoma is one of the common urological malignancies occurring worldwide in both sexes, it is one of the first cancers associated with industrialization. Therefore, it is expectedly increasing in incidence in this country.

Though the medical community has not yet succeeded in significantly lowering the incidence of this largely preventable cancer, they succeeded in improving the treatment of the disease; however, the increase in mortality emphasizes the need for further improve prevention, detection, and treatment.

For early detection, we have to be familiar with mode of presentation and epidemiological variation of the disease especially in multi racial community like Malaysia. Superficial or non-invasive bladder cancer is potentially curable with minimal invasive surgery. However, this depends on the early detection with visualization of the interior of urinary bladder by cystoscopy for those who present with haematuria, which is the commonest presenting symptom of the disease.

Urology unit in Hospital Universiti Sains Malaysia, Kubang Kerian being a tertiary referral center received most of these cases with suspected cancer bladder from the state of Kelantan and nearest states. Availability of the relevant equipments, facilities as well as the expertise allow for institution of proper surgical and other appropriate treatment modalities.

The aim of this retrospective study is to determine the disease pattern in patients with cancer bladder in hospital universiti sains Malaysia regarding age, sex and race of patients, to highlight clinical presentation and stage of disease at time of presentation, as well as cystoscopic and histopathological findings. Modalities of treatments offered in HUSM would also review.

It is hope that results of this study will enrich the local literature on various aspect of bladder cancer management in this locality.

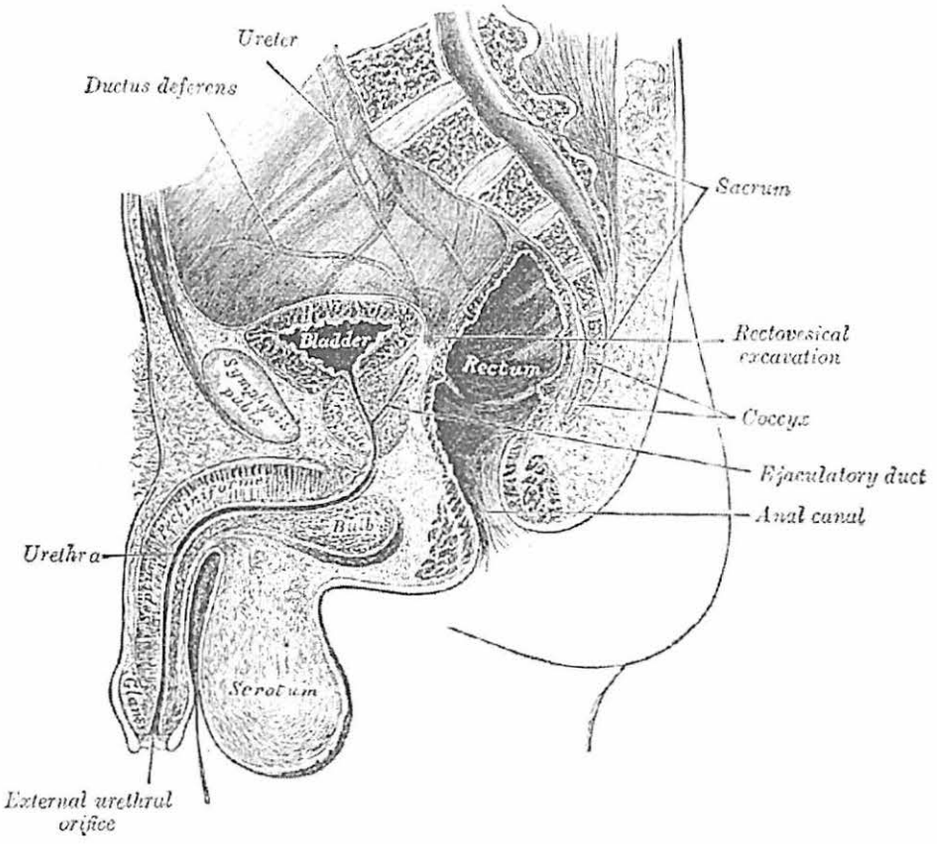
2. LITERATURE REVIEW

2.1 ANATOMY OF THE URINARY BLADDER

2.1.1 General Description

Urinary bladder is a musculomembranous sac, which acts as a reservoir for the urine; its size, position, and relations vary according to the amount of fluid it contains, age and sex. The empty bladder has the form of a flattened tetrahedron, with its vertex (apex) tilted forward. It presents a fundus, a vertex, a superior and an inferior surface. The fundus directed downward and backward toward the rectum, from which it is separated by the rectovesical fascia, the vesicule seminales, and the terminal portions of the ducts deferentes. The vertex is directed forward toward the upper part of the symphysis pubis, and from it the middle umbilical ligament is continued upward on the back of the anterior abdominal wall to the umbilicus. The superior surface is triangular, bounded on either side by a lateral border, which separates it from the inferior surface, and behind by a posterior border, represented by a line joining the two ureters, which intervenes between it and the fundus. The lateral borders extend from the ureters to the vertex, and from them the peritoneum is carried to the walls of the pelvis. The superior surface is directed upward, is covered by peritoneum, and is in relation with the sigmoid colon and some of the coils of the small intestine. The inferior surface is directed downward and is uncovered by peritoneum. The infero-lateral portions of the inferior surface are directed downward and lateralward: in front, they are separated from the symphysis pubis by a mass of fatty tissue, which is named the retropubic pad; behind, they are in contact with the fascia which covers the Levatores ani and Obturatores interni (Gray, 2000) .

(a)



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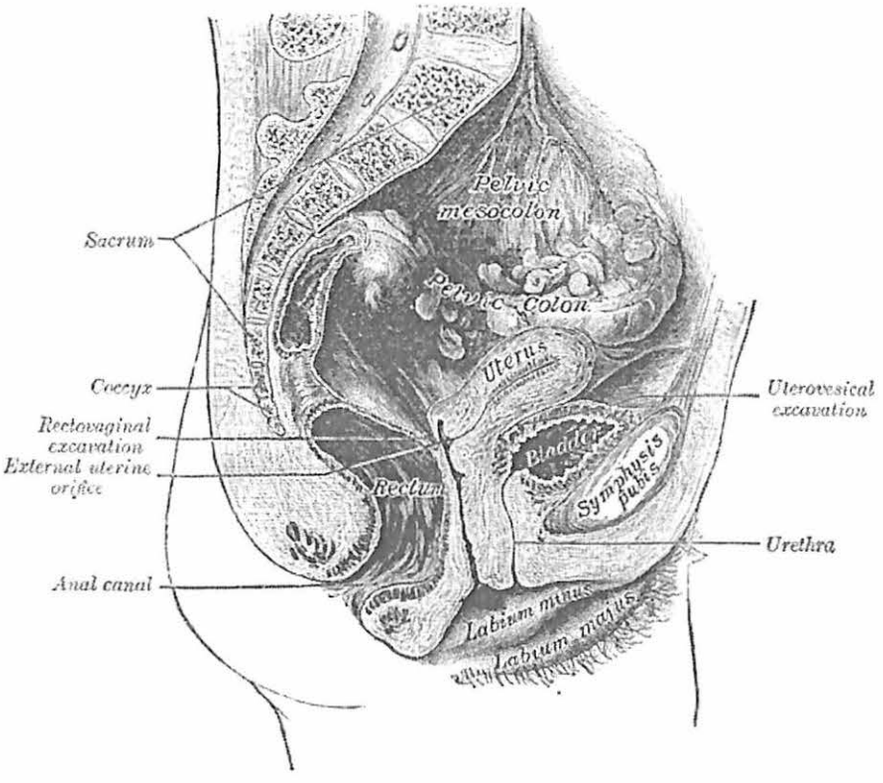


FIGURE 1: MEDIAN SAGITTAL SECTION OF THE PELVIS
(A) MALE (B) FEMALE

CITED FROM GRAY'S ANATOMY OF HUMAN BODY

When the bladder is empty, it is placed entirely within the pelvis, below the level of the obliterated hypogastric arteries, and below the level of the ductus deferentes. As the viscus fills, its fundus being less fixed, its superior surface gradually rises into the abdominal cavity, carrying with it its peritoneal covering, and at the same time rounding off the posterior and lateral borders. When the bladder is moderately full it contains about 0.5 liter and assumes an oval form; the long diameter of the oval measures about 12 cm. and is directed upward and forward.

2.1.2 The Female Bladder

In the female, the bladder is anterior to the uterus and the upper part of the vagina. It is separated from the anterior surface of the body of the uterus by the vesicouterine fossa, but below the level of this fossa it is connected to the front of the cervix uteri and the upper part of the anterior wall of the vagina by areolar tissue, this area is known as the base of the bladder. (Figure 1)

2.1.3 Interior of the Bladder

The mucous membrane lining the bladder is, over the greater part of the viscus, loosely attached to the muscular coat, and appears wrinkled or folded when the bladder is contracted. Over a small triangular area, termed the trigonum vesica, immediately above and behind the internal orifice of the urethra, the mucous membrane is firmly bound to the muscular coat, and is always smooth. Stretching behind the latter openings is a slightly curved ridge, the torus uretericus, forming the base of the trigone and produced by an underlying bundle of non-striped muscular fibers. (Figure 1-a)

When the bladder is illuminated the torus uretericus appears as a pale band and forms an important guide during the operation of introducing a catheter into the ureter.

The orifices of the ureters are placed at the postero-lateral angles of the trigonum vesica, and are usually slit-like in form. In the contracted bladder, they are about 2.5 cm. apart and about the same distance from the internal urethral orifice; in the distended viscus, these measurements may be increased to about 5 cm. (Gray, 2000).

2.1.4 Bladder Coats

The bladder is composed of the four coats (Figure 2 -b):

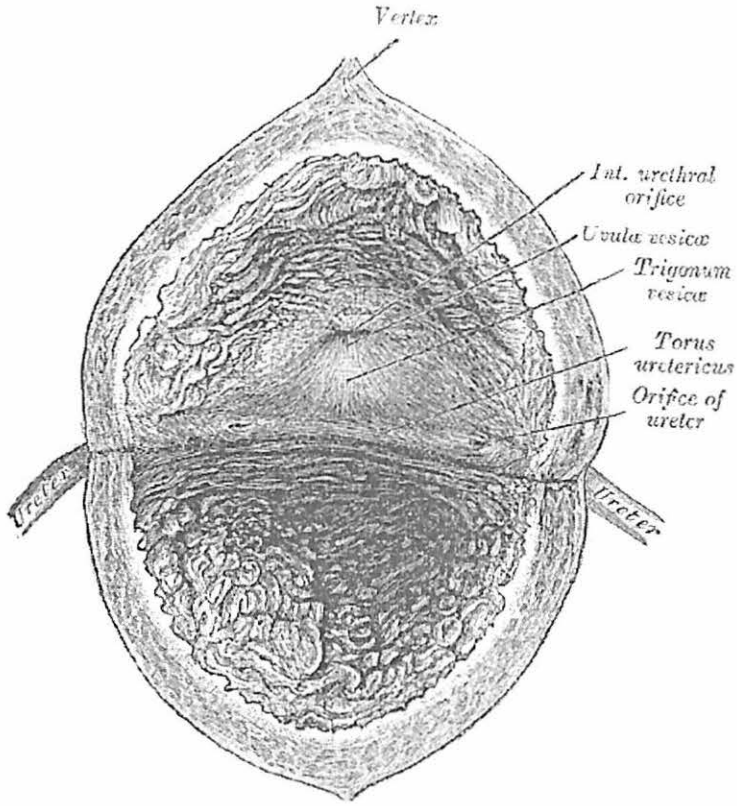
(1) The serous coat (tunica serosa) is a partial one, and is derived from the peritoneum. It invests the superior surface and the upper parts of the lateral surfaces, and is reflected from these on to the abdominal and pelvic walls.

(2) The muscular coat (tunica muscularis) consists of three layers of unstriped muscular fibers: an external layer composed of fibers having for the most part a longitudinal arrangement; a middle layer, in which the fibers are arranged, more or less, in a circular manner; and an internal layer, in which the fibers have a general longitudinal arrangement.

(3) The submucous coat (tela submucosa) consists of a layer of areolar tissue, connecting together the muscular and mucous coats, and intimately united to the latter.

(4) The mucous coat (tunica mucosa) is thin, smooth, and of a pale rose color. The epithelium covering it is of the transitional variety, consisting of a superficial layer of polyhedral flattened cells, each with one, two, or three nuclei; beneath these is a stratum of large club-shaped cells, with their narrow extremities directed downward and wedged in between smaller spindle-shaped cells, containing oval nuclei (Gray, 2000).

(a)



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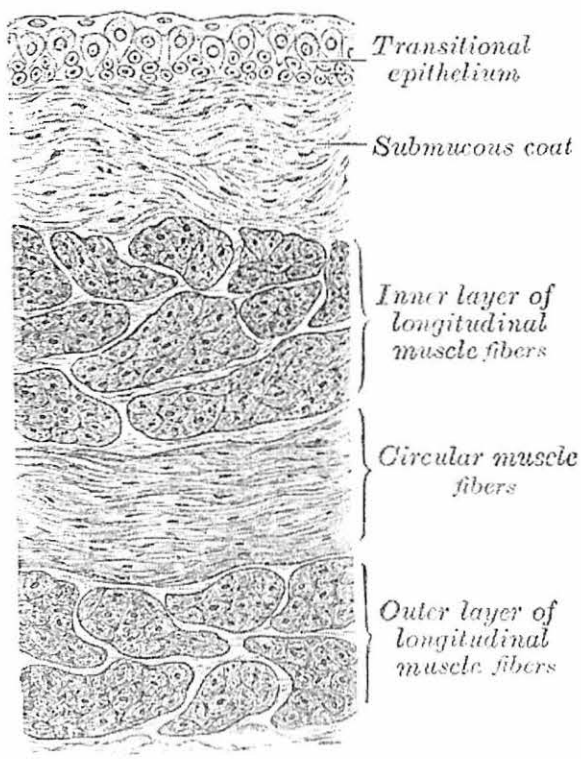

FIGURE 2: (a) INTERIOR OF THE URINARY BLADDER (b) BLADDER COATS

CITED FROM GRAY'S ANATOMY OF HUMAN BODY

2.1.5 Vessels and Nerves.

The arteries supplying the bladder are the superior, middle, and inferior vesicle, 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 Lymphatic vessels of the bladder originate in two plexuses, an intra- and an extramuscular, it being generally admitted that the mucous membrane is devoid of lymphatics. The efferent vessels are arranged in two groups, one from the anterior and another from the posterior surface of the bladder. The vessels from the anterior surface pass to the external iliac glands, but in their course minute glands are situated. These minute glands are arranged in two groups, an anterior vesical, in front of the bladder, and a lateral vesical, in relation to the lateral umbilical ligament. The vessels from the posterior surface pass to the hypogastric, external, and common iliac glands; those draining the upper part of this surface traverse the lateral vesical glands.

The nerves of the bladder are (1) fine medullated (myelinated) fibers from the third and fourth sacral nerves, and (2) non-medullated (non-myelinated) 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 (Gray, 2000).

2.2 EPIDEMIOLOGY OF BLADDER CANCER

2.2.1 Introduction

Bladder cancer constitutes the most frequent malignant neoplasia in urinary tract. The incidence, morbidity, and mortality rates associated with bladder cancer vary by country, ethnicity, gender, and age (Jemal *et al.*, 2005).

Bladder cancer, considered as one of the first cancers associated with industrialization, it is increasing in incidence in the modern world. In USA there were 63,210 newly diagnosed cases of bladder cancer and 13,180 deaths due to this disease in 2005, making it the fourth most commonly diagnosed cancer in the United States (Gwynn and Clark, 2006) , (Jemal *et al.*, 2005).

2.2.2 Age and sex distribution

According to surveillance, epidemiology, and outcome data of the United State National Cancer Institute, white individual had an incidence of 17.7 per 100,000 population, and black had an incidence of 9.2 per 100,000 population. Between 1990 and 1997, the age-adjusted incidence for Hispanics was 8.0 per 100,000 population, for Asians it was 7.5 per 100,000 and for American Indians it was 2.6 per 100,000 (Ries *et al.*, 2000).

Men have a risk that is at least three times greater than that of women. The age-adjusted incidence rate for men is 28.2 per 100,000 and for women it is 7.5 per 100,000. Moreover, the lifetime risk of having bladder cancer is 3.40% for men and 1.18% for women (Ries *et al.*, 2000).

An individual 65 years and older has an incidence of 110.8 per 100,000 population, while younger persons has an incidence of only 6.4 per 100,000 population. Statistically, the risk for a 70-year-old is two to three times greater than that for a person 55 to 69 years old, and 15 to 20 times greater than for a person 30 to 54 years old.
In the United States and Canada, an average of 11 years of life are lost per bladder cancer death.1,9 Between 1990 and 1997, White persons had an age-adjusted mortality rate of 3.3 per 100,000, while Black persons had a mortality rate of 3.1 per 100,000 (Miller *et al.*, 2006).

2.2.3 Occupational Exposure

Bladder cancer is strongly linked to occupational and environmental exposure to chemicals. The development of the disease is associated with the excretion of carcinogenic metabolites in the urine. In the early 1950s an investigation of bladder cancers in workers in British chemical industries showed that individuals exposed to aromatic amines especially benzidine and β-naphtylamine had a 30 times greater risk of developing bladder cancer than the general population. The average latent period for the development of the disease was more than 15 years (van der Meijden, 1998).

Such exposures were related to work places in the chemical industry, involving production and processing of classical aromatic amines, and in the rubber industry. Occupational bladder cancer has also been observed in dyers, painters and hairdressers. Even some occupations with much lower exposures to carcinogenic aromatic amines, like coke oven workers or workers in the rubber industry after the ban on β-naphthylamine, are at risk. In these occupations, exposure to complex mixtures of substances containing combustion products (e.g. polycyclic aromatic hydrocarbons) or nitrosamines is common (Golka *et al.*, 2004).

2.2.4 Tobacco smoking

Cigarette smoking is the leading cause of bladder cancer nowadays, with relative risk estimates averaging 3.0 across 74 epidemiologic studies. Putative carcinogenic constituents of tobacco smoke include polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, arylamines, heterocyclic amines, various epoxides and numerous others. Metabolic activation of these compounds and subsequent binding of their reactive metabolites to DNA represent key tumourigenic events(Karagas *et al.*, 2005).

Exposure of the bladder mucosal epithelium to tobacco-related carcinogens may be modulated by the activity of the glutathione-S-transferases, which are involved in the conjugation of reduced GSH with reactive electrophiles generated from tobacco smoke.(Karagas *et al.*, 2005).

Esteban and coworker found that the duration and intensity of cigarette smoking independently increased the risk of bladder cancer. They confirmed that smoking cessation reduces the risk and that the effect is proportional to the length of time interval since quitting. They detected a statistically significant difference in the risk of bladder cancer between men and women who smoked. Furthermore, they also demonstrated that, when comparable amounts of cigarettes were smoked, women who smoked had higher levels of 3- and 4-aminobiphenyl (ABP) hemoglobin adducts than men who smoked. This observation is important because arylamines (including ABPs), which are found in cigarette smoke, are believed to play a major role in smoking-induced bladder carcinogenesis (Castelao *et al.*, 2001).

2.2.5 Drugs, alcohol and dietary factors

In the Mediterranean region of France where bladder cancer mortality and incidence are high, a case-control study with 219 male incident cases and 794 randomized, male population controls was carried out in 1987-89 to investigate bladder cancer risk factors and more specifically, regional factors. This investigation confirms the role of tobacco and of certain occupational exposures in bladder carcinogenesis. There was a significant dose-response relationship with lifelong coffee drinking and alcohol consumption; however, the risk estimates were only significantly elevated for the heaviest drinkers. The intake of saccharin was not associated with risk of bladder cancer. Infrequent consumption of carrots, spinach, and marrows conferred an increased risk, suggesting a protective effect of vitamin A. Finally, this investigation results in some new hypotheses. The study of residences and birthplaces has revealed a lower risk for those who have lived in a non-Mediterranean area and a higher risk for those born in a

Mediterranean area. These features might be explained by some Mediterranean dietary habits, such as a high consumption of spices (Momas *et al.*, 1994).

2.2.6 Other factors

Chronic irritation of the bladder mucosa predisposes to the development of bladder cancer. Longstanding bladder calculi associated with BPH or indwelling catheters in those with spinal injuries are associated with an increased risk of cancer bladder and most often of the squamous cell variety. Pelvic irradiation for extravesical pelvic malignancies is another predisposing factor(Ries *et al.*, 2000).

Another potential causative agent, particularly in Africa, is Schistosoma haematobium. This parasite is presumed to cause cancer by invoking chronic inflammation and interfering with the metabolism of cigarette smoke-related bladder mutagens. Interestingly, most cancers caused by schistosomiasis are squamous cell in origin and appear in younger patient (Bedwani *et al.*, 1998).

2.3 PATHOLOGY OF BLADDER CANCER

2.3.1 Introduction

Histopathologic features of urothelial carcinoma of the bladder have prognostic significance. Recognition of invasion and of its level of penetration into the bladder wall forms the basis of pathologic staging and patient's therapy(Bircan *et al.*, 2005).

In general more than 90% of bladder carcinomas are transitional cell carcinomas derived from the uroepithelium, about 6% to 8% are squamous cell variety, and 2% are adenocarcinomas (Mostofi *et al.*, 1990).

Studies from United States, shows 85% to 95% of bladder cancers are transitional-cell carcinomas. Mixed tumours containing squamous-cell carcinoma and adenocarcinoma elements are reported at various rates between 10% and 30%. Pure squamous-cell carcinoma occurs in less than 3% of bladder cancers in the United States, but in areas where bilharziasis is endemic (eg, Egypt), squamous-cell carcinoma of the bladder is the most common malignancy (Mahamooth and Awang, 1983).

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Adenocarcinoma accounts for 2% of bladder cancers, most occurs on the trigone of the bladder. A particular subset of adenocarcinomas arising from the urachus remnant are usually locate over the dome of the bladder. About 70% to 80% of bladder cancers occur on the lateral or posterior walls of the bladder, and 20%, on the trigone. Thirty percent of tumours are multifocal at diagnosis. (Pode *et al.* ,1987).

According to another study(Mahamooth and Awang, 1983) The commonest localization of bladder cancer are the side wall of the bladder , followed by the posterior wall , the bladder neck , the ureteric orifices and the Trigone .

2.3.2 Staging of Bladder Tumour

The stage of the cancer is the most important deciding factor by which treatment will be instituted. The clinical staging of carcinoma of the bladder is determined by the depth of invasion of the bladder wall by the tumour. This determination requires a cystoscopic examination that includes a biopsy, and examination under anesthesia to assess the size and mobility of palpable masses, the degree of induration of the bladder wall, and the presence of extravesical extension or invasion of adjacent organs.

Clinical staging, even when computed tomographic and/or magnetic resonance imaging scans and other imaging modalities are used, often underestimates the extent of tumour, particularly in cancers that are less differentiated and more deeply invasive (Skinner, 1977).

The most accurate and the latest staging system is the TNM system. It is generally accepted for staging bladder tumours (Figure 3)

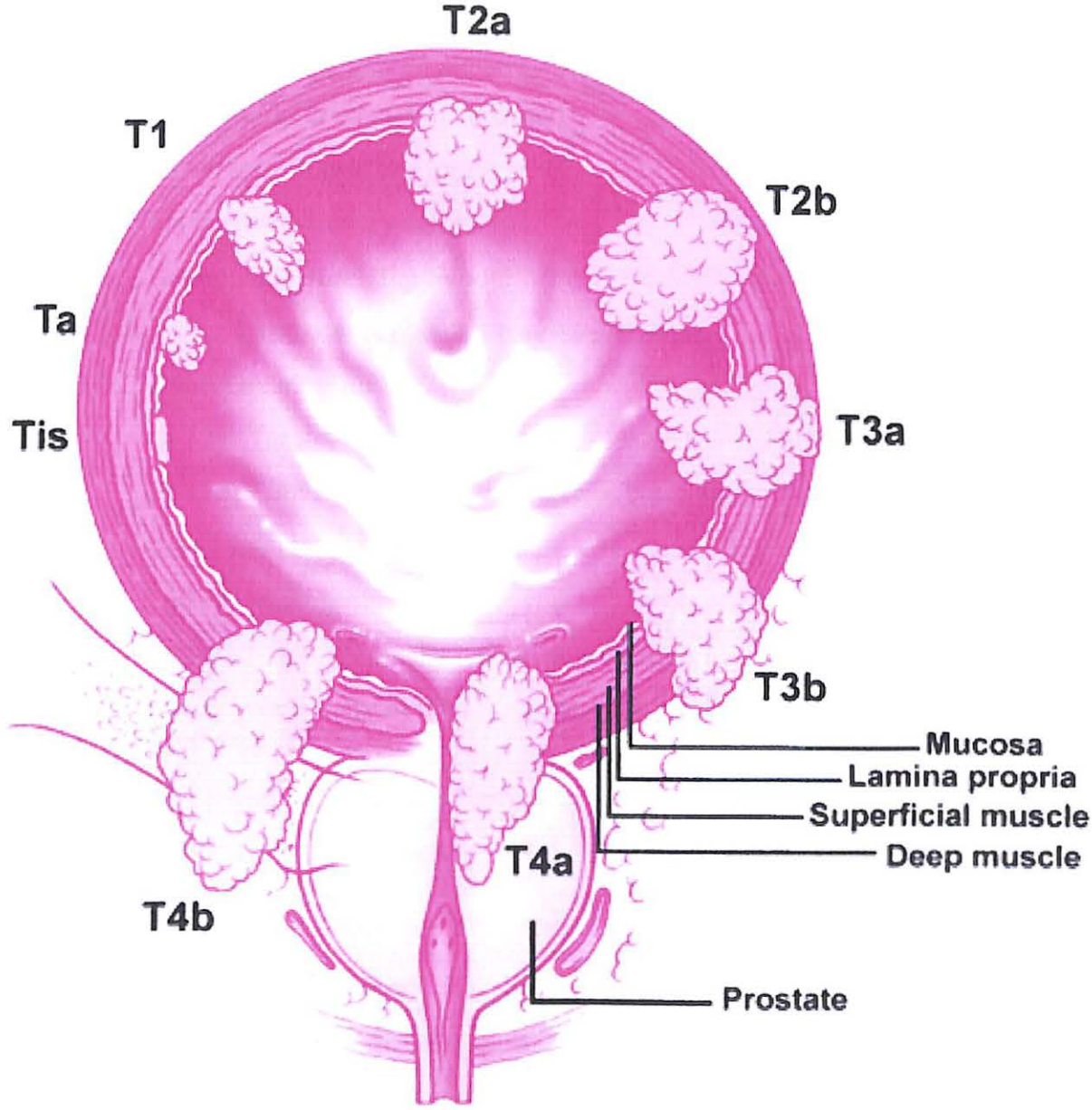

FIGURE 3: STAGING IN BLADDER CANCER,

(CITED FROM : BMJ. 1999 Mar 27;318(7187):875-6)

2.3.2.1 TNM staging of bladder cancer

Primary tumour (T)

- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- Ta: Noninvasive papillary carcinoma
- Tis: Carcinoma *in situ*: "flat tumour"
- T1: Tumour invades subepithelial connective tissue
- T2: Tumour invades muscle
  - pT2a: Tumour invades superficial muscle (inner half)
  - pT2b: Tumour invades deep muscle (outer half)
- T3: Tumour invades perivesical tissue
  - pT3a: Microscopically
  - pT3b: Macroscopically (extravesical mass)
- T4: Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall
  - T4a: Tumour invades the prostate, uterus, vagina
  - T4b: Tumour invades the pelvic wall, abdominal wall

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3: Metastasis in a lymph node, more than 5 cm in greatest dimension

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

2.3.2.2 AJCC stage groupings

Stage 0a

- Ta, N0, M0

Stage 0is

- Tis, N0, M0

Stage I

- T1, N0, M0

Stage II

- T2a, N0, M0
- T2b, N0, M0

Stage III

- T3a, N0, M0
- T3b, N0, M0
- T4a, N0, M0

Stage IV

- T4b, N0, M0
- Any T, N1, M0
- Any T, N2, M0
- Any T, N3, M0
- Any T, any N, M1

A tumour that is limited to the mucosa and lies flat is Tis (carcinoma in situ); a tumour that is papillary and limited to the mucosa is pTa and a tumour that penetrates the lamina propria but not the muscle layer is pT1. If the tumour invades muscle it may be staged from pT2 to pT4 according to the depth of infiltration of muscle tissue or the extent to which the surrounding tissue is affected. Tumours that invade the bladder muscle are highly malignant and have a strong potential to metastasise preferentially to regional lymph nodes, lungs, liver, and bone(van der Meijden, 1998). Therefore computed tomography, chest x rays, magnetic resonance imaging, and bone scanning are advised.

2.3.3 Grading of Bladder Tumour

Both the grade and stage at diagnosis of cancer bladder have extremely important prognostic and therapeutic implications.

The grade is determined by pathology tests, showing how abnormal or aggressive the cells of biopsy specimens appear , and how closely a tumour resembles normal tissue of its same type. Differentiation is another term used to describe the degree of an abnormal cell's resemblance to it's normal counterpart. Tumour cells are described as well differentiated when they look much like normal cells of the same type and are able to carry out some functions of normal cells. Poorly differentiated and undifferentiated tumour cells are disorganized and abnormal looking.

As a rule, the grade of a tumour corresponds to its rate of growth or aggressiveness. An undifferentiated or high-grade tumour grows more quickly than a well differentiated or a low-grade one. A large tumour can be low grade, a small tumour can be high grade. Carcinoma in situ is a potentially dangerous and usually high grade tumour, and CIS patients are at greater risk for progression and must be monitored closely.

The World Health Organization (WHO) classification recognizes three grades of urothelial carcinoma. Grade 1 represents well-differentiated papillary tumours with limited atypia and mitoses. At the other end, Grade 3 lesions show a marked increase in the cell layers and cell size, and noticeable pleomorphism and mitoses are prominent. Tumour grade appears to correlate significantly with the natural history of transitional cell carcinoma. The higher the grade of the diagnosis, the higher the incidence of death from the disease within two years (Herr, 1993).

Epidemiological data illustrating the distribution and topography of bladder cancer between 1990 and 1993 show that 38% of all neoplasms were G1 and G2 transitional cell carcinoma . G3 or G4 carcinoma was only seen in 23%.

Nontransitional cell histologies, however, all behave very aggressively and, in general, are less responsive to treatments other than extirpative surgery. In general, the prognoses of patients and the choice of treatments depend on the aggressiveness and grade of the tumour.

2.3.4 Genetics of Bladder Tumour

The role of oncogenes is under intense investigation. Cytogenetic analysis has provided strong evidence that loss of a suppressor gene or genes on chromosome 9 is frequently involved in the genesis of bladder cancer. Mutations of the p53 tumour suppressor gene have been identified in 50% of high-grade and stage bladder tumours, and are important in determining survival after neo-adjuvant chemotherapy on a type 3 level of evidence. Oncogenes of the ras gene family have been found in bladder cancer. A correlation has been shown between the expression of ras protein and high histological grade. In addition, an association between c-myc oncoprotein expression and recurrence or invasion in superficial tumours has been shown. Methylation of the c-myc oncogene may also correlate with stage and grade. Newer and increasingly important prognostic indicators may be utilized to select patients who stand to benefit from chemotherapy. In the context of well conducted clinical protocols, investigational prognostic factors such as DNA ploidy, p53, mdr 1, retinoblastoma gene product, NM23 RNA levels, and T138 surface antigen expression may be used to select patients for specific therapies(de Braud et al., 2002).

Expression of the tumour suppressor gene p53 also has been associated with an adverse prognosis for patients with invasive bladder cancer. A retrospective study of 243 patients treated by radical cystectomy found that the presence of nuclear p53 was an independent predictor for recurrence among patients with stage T1, T2, or T3 tumours. Another retrospective study showed p53 expression to be of prognostic value when considered with stage or labeling index (Esrig et al., 1994).

The detection of circulating tumour cells and micrometastases may have important prognostic and therapeutic implications. Because their numbers can be very small, these tumour cells are not easily detected using conventional methods. In the last decade, molecular techniques have been widely used for the detection of occult tumour cells

The molecular detection of occult tumour cells can be accomplished by PCR amplification of tumour-specific abnormalities present in the DNA or mRNA of malignant cells. The other main PCR strategy for the detection of CTC and micrometastases involves amplification of tissue-specific mRNA. This latter method was often applied to solid tumours, whereas the former was occasionally used. PCR was shown to be superior to conventional techniques in detecting occult tumour cells, allowing the identification of 1 malignant cell mixed with 1 to 10 million normal cells. In some reports, PCR is shown to be a strong predictor of outcome. The molecular detection of circulating tumour cells and micrometastases in solid tumours can be accomplished using highly sensitive PCR assays (Ghossein et al., 1999)

2.4 CLINICAL PRESENTATION

The diagnosis of bladder cancer is often delayed due to the similarity of symptoms to those of benign disorders (eg, urinary tract infection, interstitial cystitis, prostatitis, and the passage of renal calculi). Furthermore, symptoms are often intermittent.

The most common presenting symptom is hematuria, which is typically intermittent, gross, painless, and present throughout micturition. Gross, painless hematuria is a common presenting symptom of bladder cancer and occurs in 80% of cases (Mahamooth and Awang, 1983).

The degree of blood in the urine is not predictive of the probability of cancer. Microscopic hematuria is present in up to one-fifth of the general population, and benign causes are predominantly, but not exclusively, responsible. Bladder cancer can, however, mimic urinary tract infection or prostatism. Irritative symptoms are more frequently associated with aggressive bladder tumours, such as grade III carcinoma or carcinoma in situ. Fortunately, urinary cytology is positive in more than 80 percent of patients with high-grade transitional cell carcinoma (Lamm and Torti, 1996).

In an adult, especially over 50 years of age, with asymptomatic gross haematuria, microscopic haematuria, or irritative voiding symptoms, it is recommended that the diagnosis of bladder cancer be considered.

For tumours overlying the urethral orifice the presenting symptom may be flank pain or pyelonephritis from obstruction. These findings are also suggestive of invasive cancer. Symptoms of advanced disease such as pain, abdominal mass or weight loss may be present as well.

Patients with advanced bladder cancer may present with pelvic pain due to an enlarging tumour or nerve root compression. Lower extremity edema may be the result of lymphatic or venous obstruction. Patients who present with metastatic disease may have bone pain.