

## Presentation and Pathology of Urinary Bladder Cancer in Yemeni Patients

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### ABSTRACT

*This prospective study was performed to describe the presentation and the staging of bladder cancer at the time of referral which is an important factor in the prediction and prognosis of the disease. The cases were seen in urology center (Al-Thawra hospital — Sana'a) in Yemen through the period from January 2008 - October 2009. Some 132 patients included 102 males and 30 females, were evaluated regarding presentation, staging and grading. Symptoms, physical examination investigation and histopathology was done. The majority of the patients were referred from Taiz governorate (18.2 %). most patients fall in the age group 50-69 years, the male to female ratio was 3:1 and the average age was 54 years. Most of the patients (71.2%) presented with gross painless hematuria associated with irritative voiding symptoms. The most common malignant tumor of urinary bladder was transitional cell carcinoma (72.7 %), 47% (62/132) had muscle invasive tumor (T2 and T3), 30.3% (40/132) had local adjacent organ metastasis (T4). The most common grading was poorly differentiated — high grade- G3 64 cases (48.4%) and it was common mainly among the age group 50-69 years. Our study suggests that bladder cancer was referred from other governorate and private hospitals as cases of urinary bladder mass at late stage (T4) and high grade tumor. However, this situation can be further improved by adopting proper screening programs and performing appropriate investigations.*

**Keywords :** Bladder cancer, Stage, Grade, Hematuria

### INTRODUCTION

Bladder cancer is the fourth most common cancer in men accounting for 6.2% of all cancers and the eighth most common cancer in women accounting for 2.5% of all cancers. It is also the second most common urogenital tumor. It is generally a disease of older men and the male to female ratio is 2.5:1. <sup>(1,2)</sup>

Painless hematuria is the most common presenting symptom of bladder cancer and occurs in about 85% of patients. <sup>(3)</sup>

Presentation with symptoms of bladder irritability such as urinary frequency, urgency, and dysuria occurs in approximately 25% of patients and is usually associated with diffuse carcinoma in situ or invasive bladder cancer. <sup>(4)</sup>

At initial presentation, approximately 50-70% of bladder tumors are superficial—stage Tis or Ta. Invasion into the lamina propria or muscle wall is identified in a smaller number of patients, approximately 28% and 24%, respectively; regional or distant metastases are found in approximately 25%. Unfortunately, 80% of

patients with invasive or metastatic disease have no previous history of bladder cancer (Kaye and Lange, 1982). Approximately 43% of tumors are classified as grade I, 25% as grade II, and 32% as grade III (Gilbert et al, 1978). There are strong correlations between tumor grade and stage and tumor recurrence, progression, and survival (Frazier et al, 1993). Patients with low-stage, low-grade disease have a low risk (<5%) of progression to invasive disease, while as many as 40% of patients with low-stage but high-grade disease will progress with extended follow-up (Herr, 2000).

Factors that result in diagnosis being made at a more advanced stage of the disease include a possible under reporting of superficial cancers, delayed diagnosis, and/or more frequent occurrence of more aggressive variants of transitional cell carcinoma in some people. <sup>(2)</sup> The vast majority of bladder cancers are transitional cell carcinomas, although a high proportion of other bladder cancers such as squamous cell carcinoma and adenocarcinoma also occur. The relatively poor outcome of these tumors may explain some of the racial and sex differences in

bladder cancer mortality<sup>(5)</sup>. There is no uniformly accepted grading system for bladder cancer. The most commonly used systems are based on the degree of anaplasia of the tumor cells. In a consensus conference, the WHO and the ISUP (Epstein et al, 1998 ) decided to classify many of these tumors as papillary urothelial neoplasms<sup>(6)</sup>.

A strong correlation exists between tumor grade and stage, with most well differentiated and moderately differentiated tumors being superficial and most poorly differentiated ones being muscle invasive. Stage for stage, there is a significant correlation between tumor grade and prognosis; however, the correlation between tumor stage and prognosis is even stronger<sup>(7)</sup>.

A papilloma (old grade -zero) is a papillary lesion with a fine fibrovascular core covered by normal bladder mucosa.<sup>(8)</sup> Well-differentiated tumors (papillary urothelial neoplasm of low malignant potential (PUNLMP) by the WHO and the ISUP —old grade -1) have a thin fibrovascular stalk with thickened urothelium containing more than seven cell layers, with cells exhibiting only slight anaplasia and pleomorphism.<sup>(8)</sup> Moderately differentiated tumors (low-grade urothelial carcinomas in the new WHO and ISUP classification —old grade 2) have a wider fibrovascular core, a greater disturbance of the base-to surface cellular maturation, and a loss of cell polarity. Poorly differentiated tumors (high-grade urothelial carcinoma in the new WHO and ISUP system - old grade 3), have cells that do not differentiate as they progress from the basement membrane to the surface<sup>(9)</sup>.

The most commonly used staging system allows for a precise and simultaneous description of the primary tumor stage (T stage), the status of lymph nodes (N stage), and metastatic sites (M stage) (American Joint Committee on Cancer, 1997). Over-staging is relatively uncommon, but clinical under-staging may occur in up to 53% of patients<sup>(11)</sup>. T<sub>a</sub> refers to non-invasive papillary carcinoma. T<sub>1</sub> means that the tumor has invaded subepithelial connective tissues. In T<sub>2</sub>, tumor has invaded muscles, T<sub>3</sub> refers to tumor that has

invaded perivesical tissues and T<sub>4</sub> is when the tumor has invaded the prostate, uterus, vagina, pelvic wall or abdominal wall.

As there are no previous studies from our center, this study was performed to determine the presentation and the staging of bladder cancer in Yemen . Also, the results were compared with the results of other studies.

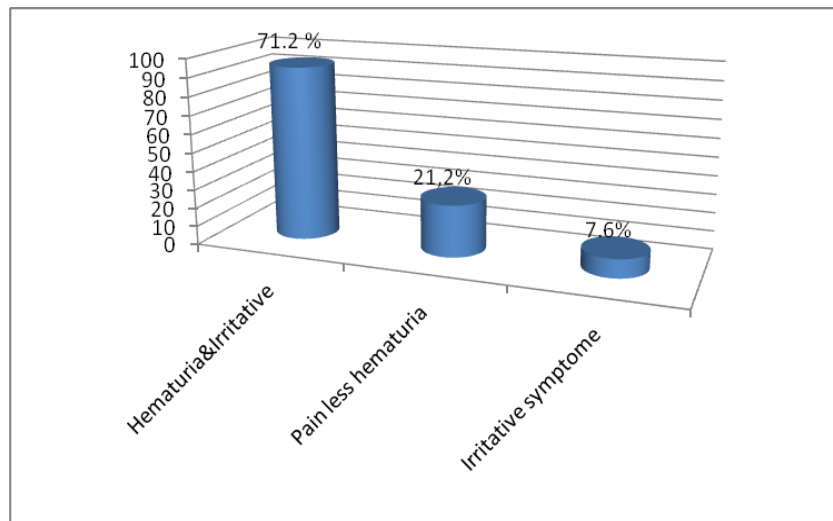
## PATIENTS AND METHODS

In this prospective study, we evaluated 132 patients with bladder cancer hospitalized at the Department of Urology and Nephrology Center, Republic of Yemen through the period from January 2008-October 2009 after informed consent was obtained . Detailed history and clinical examination in addition to relevant investigations were carried out on these 132 patients in order to diagnose bladder cancer and to determine its grading and staging. The investigations included microscopic examination of the urine, urine cytology, plain x-ray of the abdomen, chest x-ray, ultrasound of the abdomen and pelvis, intravenous urography and cystography, CT scan and/or MRI, cystourethroscopy and histopathological examination of biopsy material in our hospital was interpreted by TNM system and WHO/ISUP system for staging and grading respectively (24). The data were analyzed manually and results were compared other studies.

## RESULTS

Among the residency of our patients , most of them were referred from Taiz governorate 24 patients (18.2%), Al-Hudidha governorate 18 patients (13.6%), Sana'a governorate 16 patients (12.1%) and Hajja governorate 14 patients (10.6%). Each of Hadramout, Amran, Damar, Al-Daleh and Al-Mahweet governorates 8 patients (6.1 %) of each one Ibb 6 patients. Al-baidha and Raima 4 patients for each one. Last came Saada, Lahj and Shabwa 2 patients for each governorate.





**Figure 2:** Distribution and percent of the chief complain of patients with bladder cancer

**Table 2:** Tumor histopathology

	<i>No. of cases</i>	<i>%</i>
Muscle invasive bladder cancer	102	77.3 %
Non muscle invasive bladder cancer	30	22.7 %
Tumor grade		
1	34	25.8 %
2	34	25.8 %
3	64	48.4 %
T classification		
Ta	0	0 %
Tis	0	0 %
T1	30	22.7 %
T2	8	6.1 %
T3	54	40.9 %
T4	40	30.3 %
Stage		
I	30	22.7 %
II	62	47 %
III	40	30.3 %
ISUP/WHO (2004)		
- Papillary urothel neoplasm of low malignat potential	34	25.8 %
- Low grade cancer	34	25.8 %
- High grade cancer	64	48.4 %
- CIS	0	0 %

CIS= Carcinoma in situ

Regarding type of bladder cancer 96 patients (72.7 %) had transitional cell carcinoma, 30 patients (22.7%) had squamous cell carcinoma, and 6 patients (4.6 %) had adenocarcinoma.

There were 77% (72/94) of patients with gross painless hematuria associated with irritative symptoms had invasive tumor (T2, T3,T4) and 46.8 % (44/94) had poor differentiated tumors (G3) while 29.8% (28/94) had G2 and 23.4% (22/94) had G1. (Table-3).

**Table 3:** Correlation of chief complain to the stage and grade:

Stage	Chief complain				Total No. (%)
	Gross painless hematuria	Gross painless hematuria Associated with irritative symptoms	Irritative symptoms		
T-1	4 (14%)	22 (23%)	4 (40%)		30 (22.7%)
T-2	2 (7%)	6 (6%)	0		8 (6.1%)
T-3	14 (50%)	40 (43%)	0		54 (40.9%)
T-4	8 (29%)	26 (28%)	6 (60%)		40 (30.3%)
Total No. (%)	28 (21.2%)	94 (71.2%)	10 (7.6%)		132 (100%)
Grade					
G 1	Low grade	8 (29%)	22 (23%)	4 (40%)	34(25.8%)
G- 2	High	6(21%)	28(30%)	0(0%)	34 (25.8%)
G-3	grade	14(50%)	44(47%)	6(60%)	64 (48.4%)
Total	No. (%)	28 (21.2%)	94 (71.2%)	10 (7.6%)	132 (100%)

Concerning the staging of the tumor, the majority of our patients 47% (62/132) had muscle invasive lesions (T2/T3) , Regional (T4 tumor) metastases were found in approximately 30.3% (40/132) of patients followed by 22.7% (30/132) had tumor with invasion into the lamina propria (T1) There were no patients with carcinoma in situ or stage Ta.

Stage T1 bladder cancer was the most commonly seen stage among all age-groups in our study, but this was more so in the age-group 50 to 69 years. T2 tumor existed mainly in the age-group 30 to 49 years and 50 to 69 years, T3 tumor was more common among patients in the age-groups 50 to 69 whereas T4 was more common among patients in the age-groups 30 to 49 years and 50 to 69 years as shown in (Table 4).

**Table 4.** Distribution of bladder tumor stages according to the age groups

Age (yr.)	T1	T2	T3	T4	Total No.(%)
<30	2 (6.5%)	0	2 (4%)	0	4 (3.1%)
30-49	8 (27%)	4 (50%)	12 (22%)	16 (40%)	40 (30.3%)
50-69	18 (60%)	4 (50%)	34 (63%)	16 (40%)	72 (54.5%)
70-89	2 (6.5%)	0	6 (11%)	8 (20%)	16 (12.1%)
Total No.(%)	30 (22.7%)	8 (6.1%)	54 (40.9%)	40 (30.3%)	132 (100%)

Regarding grading , majority of the study patients 48.4% (64/132) had poorly differentiated tumor (G3). Moderately differentiated tumor (G2) was found in 25.8 % (34/132), while well differentiated tumor (G1) was found in 25.8 % (34/132) of the study patients. (Table 5).

**Table 5.** Stage and grade of bladder cancer at presentation in our study

Grade	T1	T2	T3	T4	Total No.(%)	
G-1	22 (16.6%)	0	10 (7.6%)	2 (1.5%)	34 (25.8%)	
G-2	Low grade	6 (4.6%)	2 (1.6%)	20 (15.2%)	6 (4.6%)	34 (25.8%)
G-3	High grade	2 (1.5%)	6 (4.5%)	24 (18.1%)	32 (24.2%)	64 (48.4%)
Total No.(%)	30 (22.7%)	8 (6.1%)	54 (40.9%)	40 (30.3%)	132 (100%)	

Correlation of grading with age group ; G1 bladder cancer was common seen in the age-group 50 to 69 years . G2 was found mainly in the age-group 50 to 69 years (56 %) and not found in

the age group < 30 and 70-89 years. G3 (high-grade) was found among all age-groups predominantly among the age group 50-69 years as shown in (Table 6).

**Table 6:** Correlation of bladder cancer grading according to the age groups

Age-group (years)	G 1 (PUNLMP)	G 2 (low grade)	G 3 (high grade)	Number (%)
<30	2 (6%)	0	2 (3%)	4 (3.1%)
30-49	10 (29%)	12 (35%)	18 (28%)	40 (30.3%)
50-69	18 (53%)	22 (65%)	34 (53%)	74 (56%)
70-89	4 (12%)	0	10 (16%)	14 (10.6 %)
Total	34 (26%)	34 (26%)	64 (48%)	132(100%)

PUNLMP= Papillary Urothel Neoplasm of Low Malignat Potential

## DISCUSSION

Most of patients were referred from Taiz governorate (1 8.2 %) which is probably due to the endemicity of schistosomiasis in this city. or possible underreporting of superficial cancers, delayed diagnosis, and/or more frequent occurrence of more aggressive variants.

Bladder cancer is nearly three times more common in men than in women<sup>(13)</sup>. In men, it is the fourth most common cancer after prostate, lung, and colorectal cancers, accounting for 6.6% of all cancer cases<sup>(13)</sup>. In women, it is the ninth most common cancer, accounting for 2.4% of all cancers<sup>(13)</sup>, in our study also the male to female ratio was 3:1.

Bladder cancer can occur at any age even in children. However, it is generally a disease of middle-aged and elderly people, with the median ages at diagnosis for urothelial carcinoma being 69 years in males and 71 years in females<sup>(2)</sup>, our study shows the average age at diagnosis for bladder cancer is 54 years (53.5 years for male and 57.5 years for female) and between the age 50-69 years which revealed that the disease is more common (54.6%). This age is 10-20 years less than reported in the literatures of other parts of the world<sup>(2)</sup>.

The presence of bladder cancer is usually suspected by hematuria. Patients with macroscopic (gross) hematuria have reported rates of bladder cancer of 13% to 34.5%<sup>(14,4)</sup>, globally, the most common presenting symptom of bladder cancer is pain less hematuria, which occurs in about 90% of cases. Microscopic hematuria is associated with a 0.5% to 10.5% rate of bladder cancer<sup>(15,16, 17, 18,19)</sup>.

ther large studies of patients with microhaematuria reported higher bladder cancer prevalence of 11.9- 21%<sup>(20,21)</sup>.

The presence of irritative voiding symptoms may double the risk, especially for CIS (5% vs.

10.5%)<sup>(16)</sup>. The Mayo Clinic reported that 80% of patients with CIS presented with irritative symptoms<sup>(22)</sup> or invasive bladder cancer<sup>(4)</sup>. In this study the main presenting complaint was gross hematuria associated with irritative voiding symptoms, which was the presenting symptom in 71.2% of cases while gross painless hematuria was the 1st complaint in only 21.2% and only irritative voiding symptoms in 7.6% . This different mode of presentation might be due to invasive tumor which was found in 77.3% (T2,T3,T4) of patients , this result is similar to two studies in Egypt<sup>(13, 23)</sup>.

More than 90% of bladder cancers are TCCs. At a consensus conference, the pathologists of the WHO and the ISUP preferred to term these urothelial cancers<sup>(24)</sup>. Squamous Cell Carcinoma accounts for only 1% of bladder cancers in England<sup>(25)</sup>, 3% to 7% in the United States<sup>(26,2)</sup>, but as many as 75% in Egypt<sup>(27)</sup>. About 80% of SCCs in Egypt are associated with chronic infection with *S. haematobium*<sup>(28)</sup> and Adenocarcinomas account for less than 2% of primary bladder cancers<sup>(29,2)</sup>, in Yemen urothelial cancers (TCCs) was the the most common (72.7%) histopathological type of bladder cancer followed by SCC and adenocarcinoma, 22.7% and 4.6% respectively.

Approximately 70% of bladder tumors are non—muscle invasive (Ta, T1, and CIS) at presentation. Of these, 70% present as stage Ta, 20% as T1, and 10% as CIS (30), in Yemen superficial bladder cancer represent 22.7 % present as stage T1 and 0% as Ta, while CIS not detected due to no random biopsy taken.

Invasion into muscle wall (T2) is identified in 24% regional (T3) or distant metastases (T4) are found in approximately 25% (Kaye and Lange, 1982). Almost 25% of patients with newly diagnosed bladder cancer have muscle-invasive disease, the vast majority being tumors of high histologic grade<sup>(31,32)</sup>. Study from the Punjab in

Pakistan reported, a higher incidence of muscle invasive lesions (75%)<sup>(33)</sup>. In Yemen 77.3% of patients had local advance invasive tumor (T2, T3,T4 30.3% ,40.9% and 6.1% respectively) , the vast majority being tumors of high histologic grade (46.9%) mostly in 6<sup>th</sup> and 7th decade.

Regarding to the grade Approximately 43% of tumors are classified as grade I, 25% as grade II, and 32% as grade III<sup>(34)</sup>. Using the more recent grading system, progression is observed in 5% of those with low grade tumors, 15—40% with high grade tumors while PTJNLMPs almost never demonstrate any risk of progression<sup>(24)</sup>, in our study PUNLMP 25.8% , low grade 25.8% and the high grade 48.4%. This results were identical to those from the Punjab in Pakistan, which revealed a high incidence of moderately and poorly differentiated tumors (86.8%)<sup>(33)</sup>.

There are strong correlations between tumor grade and stage and tumor recurrence, progression, and survival. Patients with low-stage, low-grade disease have a low risk (<5%) of progression to invasive disease, while as many as 40% of patients with low-stage but high-grade disease will progress with extended follow-up<sup>(3)</sup>, in our study T1/G1 16.6%, T3/G3 18.1%, T4/G3 24.2% was found among all age-groups predominantly among the age group 50-69 years which indicates the late detection of bladder cancer in Yemen.

To improve the prognoses of patients with urinary bladder cancer by early detection of the tumor by performing strategic control for the S. haematobium endemic regions including Urinary cytology and cystoscopy.

## CONCLUSIONS

Most cases of our research referred to us from other governorates with advance stages which is related to the education of the patient who ignored the gross hematuria, and the defect in the evaluation of hematuria in those hospitals therefore present late with advance stage.

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