RESEARCH COMMUNICATION

Carcinoma of the Urinary Bladder in a Tertiary Care Setting in a Developing Country

Farhana Badar*, Ambreen Sattar, Fouzia Meerza, Noureen Irfan, Neelam Siddiqui

Abstract

Background: Men have greater incidence and mortality rates than women for bladder cancer. Most bladder cancers are transitional cell carcinomas. Objectives: To determine the epidemiologic features of urinary bladder cancer cases presenting at a cancer hospital, from Dec. 1994 through Dec. 2004. Methods: Six-hundred and seven medical records were evaluated retrospectively at the Shaukat Khanum Memorial Cancer Hospital. Gender, age, histologic types, grade, stage, symptoms, risk factors, and patient follow-up were studied. Staging was done through the American Joint Commission on Cancer's criteria. Class of Case was established using the Facility Oncology Registry Data Standards, 2004. Results: Mean age: 55.5 years; men: 83%. Transitional cell- in 86%, squamous cell- in 4%, adeno- in 3%, and undifferentiated carcinoma in 7% of the cases. Stage: II in 18.3%, I in 17.3%, III in 14.2%, IV in 26%, 0 in 6.3%, and not evaluable in 17.8% of the cases. Grades: G3 in 37.9%, G2 in 25.2%, G1 in 9.7%, G4 in 2.8%, and undetermined in 24.4% of the subjects. Commonest presenting symptom: hematuria in 54.7% men and 52.9% women; risk factor: positive smoking history in nearly 35% males and 2% females. Average interval between diagnosis and last contact: 26.5 months; for analytic cases, 34.9 months. Conclusion: Urinary bladder cancer was seen primarily in males; transitional cell type was dominant. Majority of the patients were symptomatic; smoking history was recorded mostly in men. Further, improving in staging could be useful in addressing the concerns about data reproducibility over time and use for surveillance purposes.

Key Words: Urinary bladder cancer - hematuria - smoking as a risk factor

Asian Pacific J Cancer Prev, **10**, 449-452

Introduction

Urinary bladder cancer is the ninth most common cancer worldwide, accounting for two-thirds of all urinary tract cancers. Ninety percent of bladder cancers are of the transitional-cell type (Stewart and Kleihues, 2003). Smoking has been implicated in the etiology of various cancers and urinary bladder cancer is one of these (Kumar et al., 2006). All bladder tumors classically produce painless hematuria. Despite significant research into their origins and improved methods of diagnosis and treatment, neoplasms of the bladder continue to exact a high toll of morbidity and mortality. The American Cancer Society estimated that 61,420 individuals (44,690 men and 16,730 women) would be diagnosed with, and 13,060 men and women would die of cancer of the urinary bladder in 2006 (http://seer.cancer.gov).

According to the Shaukat Khanum Memorial Cancer Hospital and Research Center Statistics, cancer of the urinary bladder ranked tenth in the list of malignancies registered from 1994 to 2004. However, in adult males (> 18 years), it was found to be the eighth commonest malignancy, accounting for 5% of cancer cases (http://www.shaukatkhanum.org.pk, 2005).

In a study conducted in Pakistan from the year 1998 till 2002, carcinoma of the urinary bladder ranked fourth with an age-standardized rate of 6.8/100,000 (Bhurgri et al., 2005) and in another study, as the eight most common cancer amongst male Afghan refugees (Khan et al., 1997) settled in Pakistan.

Materials and Methods

Six-hundred and seven consecutive patients with histopathologically proven carcinoma of the urinary bladder, recorded in the disease-specific registry from 1994 to 2004, were included in this retrospective review. The disease-specific registry facilitating the Outcomes Research is an integral part of the Oracle-based Hospital Information System, which is a modern electronic repository of data from the clinical, research, and administrative sections of the Hospital. Data entry was done in the Oracle-based database and queries were run to generate collated data that were finally imputed into the Statistical Package of Social Sciences (SPSS), version 10, for further analysis. Descriptive statistics were

*Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan *For Correspondence: farhana@skm.org.pk; farhana_badar@yahoo.com*

obtained for factors as age distribution, histology, possible risk factors, and presenting symptoms, which were also stratified by gender. Disease stage, grade of cancer, class of case, and final patient status were also evaluated. The follow-up period (interval between diagnosis and last contact) was determined and the analysis of variance (ANOVA) Test was used to test the difference in the average values of follow-up time between two groups analytic and non-analytic, as described below. The test was considered to be significant at an alpha-level of 0.05.

Clinical features were further studied by a careful review of medical histories and patients were identified as having either single or multiple symptoms. Records were reviewed for the presence of possible risk factors like smoking, niswar, pelvic irradiation, occupational hazards, and *Schistosoma hematobium*. Patients were categorized as being lost to follow-up if they had been given an appointment to visit the hospital but did not make their appointment then and also did not visit the facility for at least 6-months following the appointment date.

Stage groups were created by applying the American Joint Commission on Cancer's (AJCC) staging methods (Greene et al., 2002). Case classification, using class of case, was done through the Facility Oncology Registry Data Standards (FORDS) (Phillips & Stewart, 2004). Class of case was defined as follows: Class 0: diagnosis at the accessioning facility with the entire first course of treatment was performed elsewhere or the decision not to treat made at another facility: class 1, diagnosis at the accessioning facility, and all or part of the first course of treatment performed at the accessioning facility; class 2, diagnosis elsewhere, with all or part of the first course of treatment performed at the accessioning facility; class 3, diagnosis and all of the first course of treatment performed elsewhere. The point to be noted is that even in those cases in which the preliminary diagnosis was made elsewhere, slides were re-examined at SKMCH & RC and diagnosis verified at the Hospital. However, for the purpose of this study, such cases were included in class 2.

Results

A total of 607 records were reviewed. Eighty-three percent of the cases (505) were male, with the male to female ratio being 5 to 1. Mean age at presentation was 55.5 years. In men, the average age at presentation was 56 years, with the median being 57 years, and mode being 60 years (7.5%) whereas, in women, the mean age was 55 years, median was 56 years, and mode, 45 years (10.8%). Of the total cases, 46 had undifferentiated carcinoma. The most common histological sub-type was transitional-cell carcinoma (TCA) documented in 86% of the cases (Table 1); 84.4% of the transitional-cell type was seen in males. In men, 87% had the transitional-cell type and in women, 82% had this type. Squamous-cell and adenocarcinoma were recorded in 6.4% of the 607 cases. Stage II was the commonest stage and seen in 18.3% of the patients, whereas, stage I was found in 17.3%, stage III in 14.2%, non-metastatic stage IV in 13.7%, metastatic stage IV in 12.5%, and stage 0 in 6.3% of the patients. In 17.8% of the patients, cancer staging could not be done due to incomplete workup. Further, histologic grade was not available in 23.1% of the cases; 37.9% presented with grade 3, 25.2% with grade 2, 9.7% with grade 1, 2.8% with grade 4, and in 1.3% grade could not be assessed.

Table 1. Histologic Sub-types of Bladder Cancer seen at SKMCH & RC

Histologic sub-type	Male	Female	Total	%
Transitional-cell carcinoma	441	81	522	86.0
Squamous-cell carcinoma	16	7	23	3.8
Adenocarcinoma	13	3	16	2.6
Undifferentiated carc, NOS	35	11	46	7.5
Total	505	102	607	100

Table 2. Data on Presenting Symptoms and Risk Factors in Bladder Cancer Patients

Symptoms/Factors	Males		Females	
	Count	%	Count	%
Single symptom				
Hematuria	276	54.6	54	52.9
Frequency of micturition	17	3.4	5	4.9
Dysuria	8	1.6	4	3.9
Multiple symptoms				
Hematuria and dysuria	46	9.1	6	5.9
Hematuria and micturition	40	7.9	7	6.9
Hematuria, dysuria, micturition	23	4.6	4	3.9
Dysuria and micturition	6	1.2	0	0
Not available	89	17.6	22	21.5
Risk factors				
Smoking*	176	34.8	2	2
No risk factor†	105	20.8	43	42.2
Niswar	9	1.6	3	2.9
Smoking and niswar‡	9	1.8	1	1
Tobacco chewing	4	0.8	1	1
Pelvic irradiation	1	0.2	3	2.9
Occupational hazard§	2	0.4	0	0
Schistosoma hematobium	0	0	0	0
Not available¶	199	39.4	49	48

*One patient reported being a smoker and having worked in a shoe manufacturing industry; †It was specified in the records that there was no risk factor especially smoking; ‡One patient reported having taken niswar and chewing tobacco; §Worked in a textile mill and pesticide factory

A study of the presenting symptoms recorded hematuria as the most common single manifestation reported in 54.7% of the male and, 52.9% of the female cohort. Remaining patients presented with a combination of symptoms as hematuria, dysuria, and frequency of micturition (Table 2). A search for possible risk factors showed that smoking history was positive in 34.8% of men and was negligible in women (2%). A small proportion of individuals reported having taken tobacco in other forms whereas, few revealed having worked in an industry (textile, shoe, pesticide) (Table 2).

All 607 cases were assigned a class of case based on the nature of involvement of the facility in the care of the patient. Accordingly, of the total, 0.3% (2/607) were grouped into class 0, 4.6% in class 1 (27/607), 44.5% in class 2 (270/607), 44.6% in class 3 (271/607), and 5.9% in class 9 (36/607). When the study ended, 22% (134/607) were still on follow-up, 13.8% (84/607) deaths had been recorded, and 32% (195/607) patients were

categorized as being lost to follow-up; 31.8% (194/607) had visited the hospital only once or twice. The mean follow-up time of 607 patients was 26.9 months. A study of analytic cases (Class 0-2) revealed the average follow-up time to be 34.9 months compared to 19.1 months for non-analytic cases. The difference was statistically significant at an alpha-level of 0.05 ($F=41.2$, $df=1$, $p<0.001$).

Discussion

Urinary bladder cancer is a disease of the elderly with most cases occurring above the age of 50 years. In our patient cohort, the mean age at presentation was 55.5 years with the male to female ratio being 5 to 1, which is similar to with what has been recorded in other studies conducted in Pakistan (Ullah et al., 2001; Ahmed et al., 2002). Globally, one of the most striking epidemiologic features has been the gender-related difference in incidence with the male to female ratios being documented as 4 to 1 in the United States and 7 to 1 in Italy (Schatte et al., 2000) and, in Spain, 6.7 to 1 (Puente et al., 2003). In addition, histopathologic and treatment differences have been recorded in the two genders (Hickey & Soloway, 1988). The male predominance appears to be related mainly to the greater prevalence of smoking and exposure to occupational carcinogens. Although, it was previously thought that women had innate factors, as hormonal influences, that protected against bladder tumor formation, more recent data demonstrate that women are at least as susceptible as men to developing bladder cancer, given comparable exposures and risk factors (Castelao et al., 2001). This has to be looked into in our population.

Further, as has been seen in other studies (Ullah et al., 2001), in our study, transitional-cell carcinoma was diagnosed as the most common histological sub-type (86%) followed by squamous-cell carcinoma (3.8%), and adenocarcinoma (2.6%). Moreover, grade III (most malignant) was most commonly seen (37.9%) in our patient cohort. In another study done at the Aga Khan University Hospital, Karachi, (Ahmed et al., 2002), grade III was found in 29.5% of the cases. The encouraging finding in our study was that many patients (nearly 43%) presented either in stage I or II. The weak point of the study is that nearly 18% of the cases could not be staged through the AJCC staging method. Therefore, the use of Collaborative Staging (CS), which is a method between the AJCC TNM (Tumor, Node, and Metastasis) staging system and the SEER (Surveillance, Epidemiology, and End Results) Extent of Disease (EOD) and Summary Staging System, could be effective in helping to increase the proportion of cases that can be staged. Collaborative Stage allows combined pathological and clinical "mixed" or "best" stage to be captured and looks promising in a setting where all classes of patients are registered at a hospital.

This being a single institution study, included all cases that might have been diagnosed/treated elsewhere or at SKMCH & RC (accessioning facility), as is mentioned in the results section above. However, an analysis of cases diagnosed at, and/or having received any of the first course of treatment at, SKMCH & RC (Class 0-2; 300 analytic cases) computed a higher follow-up time than all cases combined together. This may be used an indicator to highlight the quality of treatment given at the hospital.
The management of bladder cancers at SKMCH & RC is as follows: For superficial cancers in low-risked patients, Transurethral Resection of the Bladder Tumor (TURBT) followed by cystoscopy every 3 months for first two years, every 6 months for the next 2 year, and thereby once yearly. In high-risked patients, TURBT and intravesical BCG are used concomitantly. For tumors that have invaded the muscle wall, radical cystectomy with ileal conduit is one choice and maximal debulking with TURBT followed by chemoradiation is another.

To date, an adequate tool for screening urinary bladder cancer has not been established. Under these circumstances, the symptomatology of disease, including hematuria, remains important both for clinicians and patients. Hematuria was, by far, the most common presenting symptom in our study as well as in other studies (Ahmed et al., 2002; Sørensen et al., 1986; Ullah et al., 2001). Hematuria in bladder cancer is generally painless, intermittent, gross, and presents throughout micturition. It should be regarded as being indicative of bladder cancer until proven otherwise (Russel et al., 2000). Dysuria is seen more often with high-grade tumors, perhaps, as a result of involvement of the bladder wall (Rosai, 1996). Pain is usually the result of locally advanced or metastatic tumor. Irritative voiding symptoms (dysuria/urgency) and obstructive voiding symptoms (straining/nocturia) were also seen in our patient cohort. In particular, irritative symptoms that include the complex of dysuria, frequency, and urgency may be highly suggestive of bladder carcinoma in-situ while obstructive symptoms may be due to tumor location at bladder neck or prostatic urethra (Heney et al., 1983). Studies are underway to check the ability of home hematuria screening in detecting bladder cancer at an early stage in the history of the disease (Ullah et al., 2001). Messing and colleagues (1995) have concluded that home hematuria screening detects high-grade bladder cancer before they start invading the muscle (Messing et al., 1995).

Development of bladder cancer is dependent on a combination of environmental and genetic factors. The incidence of carcinoma of bladder resembles that of bronchogenic carcinoma, being more common in males than females and in industrialized than in developing nations if the world (Kumar et al., 2006). Besides the lung, the bladder is another recognized site susceptible to carcinogenesis attributed to tobacco. In our study, history of risk factors was available in 407 cases only. Smoking was the most common risk factor reported in our patient cohort. It has been documented that smoking increases the risk of bladder cancer three- to seven- folds depending on the pack-years smoked and smoking habits (Kumar et al., 2006) has complemented the epidemiologic evidence of a dose-response relationship of cigarette smoking and urinary bladder cancer (Auerbach & Garfinbkel, 1989). Castelao and colleagues (Castelao et al., 2001) have confirmed previous reports that smoking cessation reduces the risk of bladder cancer and the effect is proportional to

the length of time interval since quitting. However, the weakness of our study is that information on the number of cigarettes smoked, person-years of smoking, and smoking cessation could not be captured as it was not available in the records.

Bladder cancer has been classified as an industrial disease since 1953 (Russel et al., 2000). Exposure to chemicals used in the aluminum, dye, paint, petroleum, rubber, and textile industries has been estimated to account for up to 20% of all bladder cancer cases (Stadler, 1993). However, history of exposure to occupational toxins was available in three cases in our study. Further, history of schistosomiasis was not found in our patient group although, schistosomiasis or bilharziasis caused by *Schistosomiasis hematobium* is endemic in Africa, Egypt, southern tips of Europe and Japan (Amonkar et al., 2001). As has also been seen in our study, urinary bladder cancer is diagnosed more commonly in old age and in males. Exposure to tobacco smoke is incriminated in the etiology of the disease, especially in males. Painless hematuria is a classical presentation and, should therefore, be investigated thoroughly. Patients diagnosed with superficial bladder cancer who have not undergone total cystectomy are at high risk for recurrence and bladder surveillance with cystoscopy is recommended for such patients every 3-6 months (Schrag et al., 2003). This, once again, highlights the need to set up a health education and promotion unit that can assist in creating awareness about early diagnosis of cancer in the population at large.

Acknowledgment

The abstract was presented at the 135th American Public Health Association Annual Meeting and Exposition, Nov. 3-7, 2007 in Washington, DC in the Cancer Epidemiology Session 2 (5108.0) with the abstract number being149369. The authors would therefore like to thank the SKMCH & RC Senior Management and the APHA for enabling them to present their findings. The authors would also like to thank the Cancer Registry and Clinical Data Management staff for their input in establishing the class of case categories, Dr. Shahid Hameed for his useful comments as a scientific reviewer on the paper, and Muhammad Neaman Siddique for validating the references in the paper.

References

Ahmed Z, Muzaffer S, Khan M, et al (2002). Transitional-cell carcinoma of the urinary bladder - a histopathological Study. *J Pak Med Assoc*, **52**, 396-8.

Amonkar P, Murali G, Krishnamurthy S (2001). Schistosoma induced squamous cell carcinoma of the bladder. *Indian J Pathol Microbiol*, **44**, 363-4.

Auerbach O, Garfinbkel L (1989). Histological changes in the urinary bladder in relation to cigarette smoking and use of artificial sweeteners. *Cancer*, **64**, 983-7

Bhurgri Y, Bhurgri A, Pervez S, et al (2005). Cancer profile of Hyderabad, Pakistan 1998-2002. *Asian Pac J Cancer Prev*, **6**, 474-80.

Castelao JE, Yuan JM, Skipper PL, et al (2001). Gender-and smoking-related bladder cancer risk. *J Natl Cancer Inst*, **93**. 538-45.

Greene FL, Page DL, Fleming ID, et al (eds) (2002). Urinary bladder. In: AJCC Cancer Staging Handbook from the AJCC Cancer Staging Manual, 6th edition. New York: Springer-Verlag, pp. 367-373.

Heney NM, Ahmed S, Flanagan MJ, et al (1983). Superficial bladder cancer: progression and recurrence. *J Urol*, **130**, 1083-6.

Hickey D, Soloway MS (1988). Does invasive bladder cancer differ between women and men? *Urology*, **32**, 183-5.

Khan SM, Gillani J, Nasreen S, Zai S (1997). Cancer in Northwest Pakistan and Afghan refugees. *J Pak Med Assoc*, **47**, 122-4

Kumar V, Abbas AK, Fausto N (eds) (2006). The lower urinary tract. In: Robbins and Cotran Pathologic Basis of Disease. 7th edition. Philadelphia: Saunders Co, pp. 1028-1032.

Messing EM, Young TB, Hunt VB, et al (1995). Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations; discussion. *Urology*, **45**, 387-96, discussion 396-97.

National Cancer Institute-SEER (2006). Cancer stat facts sheet; urinary bladder cancer: http://seer.cancer.gov/

Phillips JN, Stewart AK (editors) (2004). Section One: Case Eligibility and Overview of Coding Principles (Revised 01/04). In 'FORDS-Facility Oncology Revised Data Standards-Revised for 2004'. Commission on Cancer, Approvals Program/Multidisciplinary Program, American College of Surgeons, pp. 1-28L.

Puente D, Malats N, Cecchini L, et al (2003). Gender-related differences in clinical and pathological characteristics and therapy of bladder cancer. *Eur Urol*, **43**, 53-62.

Rosai J (editor) (1996). Urinary tract. In: Ackerman's Surgical Pathology, 8th edition. St. Louis: Mosby, pp. 1195-6.

Russell RCG, Williams NS, Bulstrode CJK (editors) (2000). The Urinary Bladder. In: Bailey and Love's "Short Practice of Surgery", 23rd edition. London: Arnold, pp. 1227-29.

Schatte E, Grunenfelder J, Fradet Y, Miles BJ (2000). Epidemiology of bladder cancer. In: Comprehensive Textbook of Genitourinary Oncology, 2nd edition. Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, editors. Philadelphia: Lippincott, Williams and Wilkins, p. 283.

Schrag D, Hsieh LJ, Rabbani F, et al (2003). Adherence to surveillance among patients with superficial bladder cancer. *J Natl Cancer Inst*, **95**, 588-97.

Shaukat Khanum Memorial Cancer Hospital and Research Center (2005). Cancer statistics, Annual cancer registry report: http://www.shaukatkhanum.org.pk/

Sørensen BL, Barlebo H, Bay-Nielsen H, et al (1986). The Copenhagen bladder cancer project 1. *Dan Med Bull*, **33**, 151-4.

Stadler WM (1993). Molecular events in the initiation and progression of bladder cancer. *Int J Oncol*, **3**, 549-57.

Stewart BW, Kleihues P (editors) (2003). Bladder cancer. In: 'World Cancer Report'. Lyon: IARCPress, pp. 228-231.

Ullah R, Nusrat J, Hamdani SR, Burdy GM, Khurshid A (2001). Cancer urinary bladder-5 year experience at CENAR, Quetta. *J Ayub Med Coll Abottabad*, **13**, 14-6.