ORIGINAL ARTICLE

An Epidemiological Study of Cases of Urothelial Carcinoma of Urinary Bladder in a Tertiary Care Centre

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Abstract:

Background: Urinary bladder cancer is the fourth most common malignancy in Western world. It is a heterogeneous disease with variable natural history. There is paucity of data in our country. *Aims and Objectives:* The present study aims to assess the risk factors contributing to urothelial carcinoma of bladder in the southern region of West Bengal and histopathological grading (WHO/ISUP). *Materials and Methods:* It was a retrospective study by multivariate analysis of case record proforma (CRP), agreed upon by a team of experts from the departments of Urosurgery and Pathology, CNMC&H, Kolkata from December, 2007 to November, 2009. Total 88 subjects who had attended in the department of urosurgery and already been diagnosed either by cystoscopic biopsy or Transurethral Resection of Bladder Tumour (TURBT), were enrolled. *Results:* There was male preponderance (86.4 % male vs 13.6 % female); the age range being 30-81 years (median 65). Hindus (81.8 %) were affected more compared to Muslims (18.2 %). Blood group analysis showed highest incidence in B group (41%) followed by O (32%). Tobacco smoking (75% cases) revealed a strong relationship with bladder cancer and that was quantity and duration dependant. Less water intake (53.4%) and poor socioeconomic status (82%) were significant contributory factors. Analysis of occupational factors gave no epidemiological clue. Histopathological Examination (HPE) revealed low grade urothelial carcinoma (51 cases), high grade (24 cases) and papilloma with low malignant potential (13 subjects). *Conclusion:* Proper epidemiological survey plays a pivotal role in bladder cancer to validate it in the disease control programme.

Keywords: Bladder Cancer; Urothelial Carcinoma, Epidemiological risk

Introduction:

Urothelial carcinoma of urinary bladder cancer is the fourth most common cancer in men and eighth most common malignancy in women in Western world [1]. The overall incidence of bladder carcinoma has increased by 10% since last 30 years and 5 years survival rate has increased by 50% in European countries [1]. It is a heterogeneous disease with variable natural history which is not yet fully explored. But an understanding of the risk factors may have more impact in prevention of the disease. Among the various known risk factors, cigarette smoking is the most important and responsible for 48% cases of bladder cancer in men and 32% in female in USA [2]. The present study intends to explore the possible risk factors due to paucity of data in our country.

The aim of this study is to assess the epidemiological factors contributing to the urothelial

carcinoma of bladder in the southern region of West Bengal and histopathological grading as per the classification of urothelial neoplasms of the urinary bladder [3] according to World Health Organization (WHO) and the International Society of Urological Pathologists (ISUP).

Material and Methods:

During two years (December 2007 to December 2009), total 88 subjects, with the diagnosis of bladder cancer, attending in the department of Urosurgery, Calcutta National Medical College and Hospital were taken for the study. They were diagnosed by histopathological examination (HPE) of tissue obtained either by cystoscopic biopsy or transurethral resection of bladder tumor (TURBT) by Urosurgeon. Each case was recorded in a Case Record Proforma (CRP), agreed upon by a team of experts from the departments of Urosurgery and Pathology. It was a retrospective study done by multivariate analysis of the CRPs of the patients treated in the institute.

Results:

The age range of the study population Table 1 was 30-81 years (median 65). Table 2 depicts epidemiological risk factors.

Table 1: Age group of the subjects

Age Range (yrs)	Number of Patients
30-39	06 (6.9%)
40-49	16 (18.2%)
50-59	24 (27.2%)
60-69	31 (35.2%)
70-79	09 (10.2%)
80-89	02 (2.2%)

Table 2: Epidemiological factors

Total (n-88)		(100%)
Sex:		
Male	76	86.4
Female	12	13.6
Religion		
Hindu	72	81.8
Muslim	16	18.2
Habit:		
Smoker	66	75
Non-smoker	22	25
Daily Water Intake:		
<4 glass	47	53.4
>4glass	41	46.6
Diet:		
Non-vegetarian	66	75
Vegetarian	22	25
Socioeconomic Status:		
Poor	72	81.8
Middle	14	15.9
Upper	2	2.2
History of UTI:		
Present	5	5.6
Absent	83	94.3
Blood Group:		
B	36	40.9
A	28	31.8
O	21	23.8
AB	3	3.4
Occupation:		
Labourers	44	50
Driver	10	11.3
Housewife	12	13.6
Others	22	25

There was male preponderance (86.4 % male vs. 13.6 % female); Hindus (81.8 %) were affected more compared to Muslims (18.2 %). Blood group analysis showed highest incidence in B group (41%) followed by O group (32%). Tobacco smoking (75% cases) revealed a strong relationship with bladder cancer and that was quantity and duration dependant [1,2]. Less water (less than four glasses of water amounting to 800 ml approx per day) intake (53.4%) and poor socioeconomic status (nearly 82%) were significant contributory factors. Subjects came from different occupations, the highest being the labourers (50%). Occupations gave no epidemiological clue. History of UTI was noted only in 5.6% of cases. Painless hematuria was the commonest presentation and sometimes dysuria in advanced cases.

Morphologically majority of the growth was exophytic (96%) showing papillary configuration and histological urothelial CA (Transitional Cell Carcinoma-TCC) which was commoner in men than in women. Sites of lesion were mostly found in posterior wall (53%), followed by lateral wall (43%) and trigone (3%). HPE revealed low grade urothelial carcinoma in 51 cases, high grade TCC in 24 cases and papilloma with low malignant potential in 13 subjects. Histopathology delineated low grade TCC with or without muscle invasion in 58%, high grade TCC with muscle invasion in 27.2% and papilloma with Low Malignant Potential in 14.8% (Fig. 1).

Statistical Analysis:

Data obtained were analyzed using SPSS software (version 16) (SPSS Inc., Chicago, III, USA). Categorical data (comparison of sex, religion, habit, daily water intake, diet, socio-

Fig. 1: Percentage of different grading of histopathology

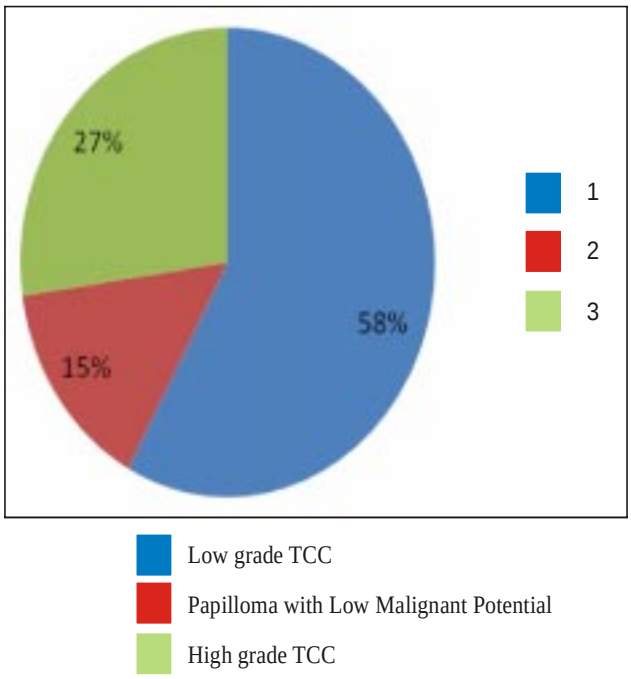


Fig. 2, 3 and 4 illustrated the histopathological features of different grades of urothelial carcinoma.

Fig. 2: High grade TCC [Low power (10x ×10x), H and E stain]

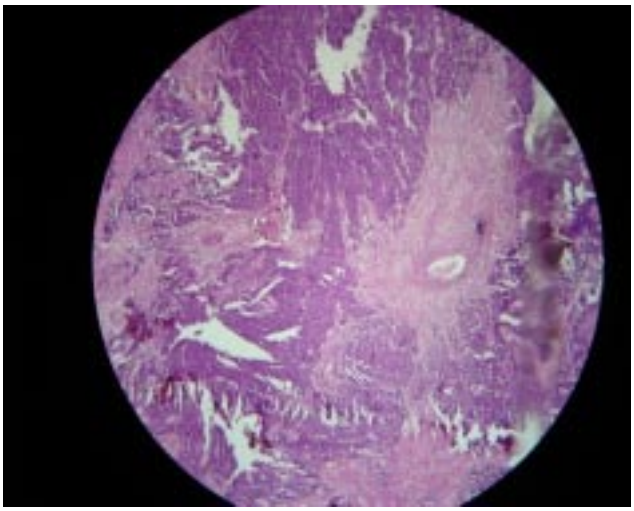


Fig. 3: Low grade TCC [High power (10x ×40x), H and E stain]

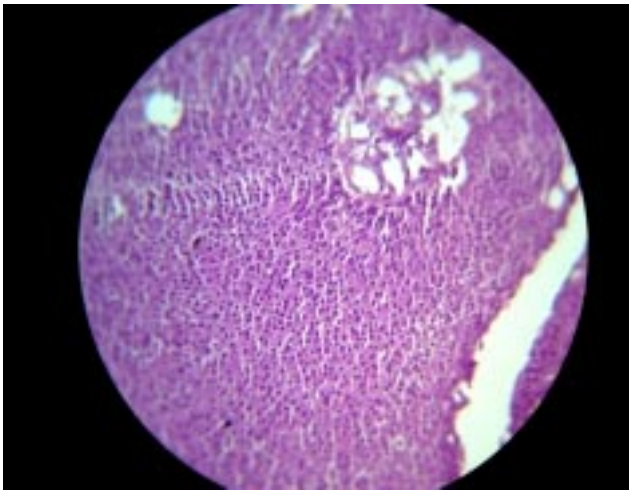
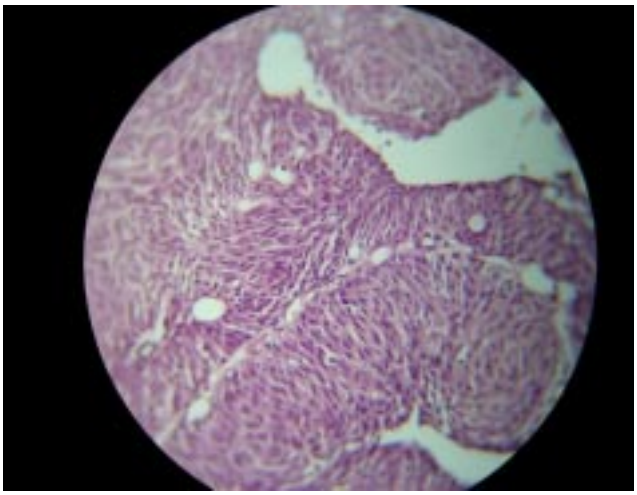


Fig. 4: Papilloma with Low Malignant Potential (HP 10X×40X), H and E Stain



economic status, history of UTI, blood group and occupation) were compared by chi-square. P values of all the variables were >0.05 and were considered to be statistically non-significant. Apparently those were the important contributory risk factors as per other studies [5, 10, 11-16]. To evaluate it properly, we need large multicentric studies.

Discussion:

The median age of bladder cancer is 65 to 70 years [1]. The present study also noted maximum numbers of cases are between 60-69years, though 1/4th of the subjects were below 50 years of age. It has been observed that grade of the lesion had no age–specific relationship; high grades of TCC were found in 36-40 years aged subjects whereas low grades in older population.

Bladder cancer is 6 times higher in males in the present study which is at par with Mungan et al [4] who found it 3 to 4 times more common in men than in women. It has been suggested that the stage-adjusted survival of bladder cancer in women is worse than in men [4]. The excess frequency of bladder cancer in men versus women is explained by smoking habits of men and estrogen-progesterone hormonal influence in the female reproductive life. Surveys [5-7] suggest that parous women have a lower risk of bladder cancer than nulliparous women. But the present studty failed to include the factor. Furthermore, in animal experiments, rats treated with androgenic hormones developed more bladder tumors than do animals treated with estrogenic hormones [8]. It is therefore suggested that androgenic hormones as opposed to estrogen may stimulate or do not inhibit oncogenesis. We find the disease more in Hindus (5 times) than Muslims; though 90% of the study population covered rural areas of South 24 Parganas having predominant muslim population (Muslim being nearly 34% in comparison to other districts of the state where it is 11 to 19% as per census 2001). No other study has shown any religious variation but some literatures opine that African Americans have only half the risk of white European Ameri-

cans [9]. It is therefore postulated that racial biologic variations and within-race individual differences also may modify various phases of carcinogenesis, such as the capacity to convert procarcinogens to carcinogens, to detoxify carcinogens, and to repair DNA.

No race factor was identified in the study. Although it is well recognized that cigarette smoking is the most important risk factor for bladder cancer on a population basis, additional factors play a role in modifying the risk posed by the smoking. History of tobacco smoking is present in 78.9% males and 25% females in the series. It depends on amount and duration as it is observed throughout the world [2]. There are populations with high smoking rates but low bladder cancer rates [10]. This suggests differences in the metabolism of smoking-related carcinogens. For example, individuals with *N*-acetyltransferase-2 slow acetylators as compared to rapid acetylators are known to have a higher risk of bladder cancer [11]. Exogenous agents (such as vitamins C and E intake) may modify the susceptibility to smoking induced bladder cancer as well.

Familial bladder cancer is a fairly rare phenomenon compared with the familial occurrence of cancer in many other tumor sites. Numerous case reports describe familial clustering of urothelial carcinoma and early age of onset suggesting a genetic component [12]. Only a few epidemiologic studies specifically address familial bladder cancer, Goldgar *et al* [13]. We therefore tried to explore the relationship between blood group and TCC but it remains inconclusive due to small sample size.

It has been estimated that occupational exposures may account for as much as 20% of all bladder cancer [14]. Exposure to naphthylamine, 4-aminobiphenyl (ABP), and benzidine, principally among workers in the textile dye and rubber industries are the only specific agents that have been unequivocally associated with bladder cancer [15]. In fact, many occupations have been marked as potentially high risk. The authors observed maximum number (50%) of bladder cancer among labourer and industry workers including employees of leather and textile factories, hair-dye handlers (barber) and shoe-makers. But the limited sample size does not give any significant epidemiological clue. Carcinogenesis in these cases thought to be a result of exposure to possible carcinogenic constituents of paints and solvents. The risk of bladder cancer among workers, especially in industries should therefore be monitored continuously. Though the present study did not find any occupational relationship since the subjects were not exposed to typical jobs.

People having non-vegetarian diet ($3/4^{th}$ of cases) and poor water intake (almost half of the cases) are the victims of TCC. This can be explained by their poor socio-economic status (82% of the study population) who cannot afford balanced diet lacking anti-oxidants like fruits and vegetables. They rather consume bulk of fish what is cheaper in this district surrounded by water bodies. High Arsenic level in water may be one of the risk factors which could be included in the study. Chronic urinary tract infection (UTI) is associated with the development of bladder cancer, especially invasive squamous cell carcinoma [16]. We observed in 5.6% cases.

Limitation:

The study failed to include control population but highlighted the key factors having impact in the causation of bladder cancer of 88 subjects. To calculate statistical significance after having enough power of the study, it should have surveyed the different characteristics in the general population of the area.

Conclusion:

The true natural history of bladder cancer is not yet fully known. Every effort has been made to explore epidemiological risk factors, and for appropriate diagnosis along with staging and grading. The study suggests that epidemiological survey should be incorporated in the evaluation of bladder cancer to formulate any disease control programme. However, large well designed prospective multicentre studies are needed to standardize the protocol.

References:

1. Cancer Incidence in Five Continents. Vol .VIII (155). Lyon, France, IARC Publications, 2002. Edited by D.M. Parkin, S.L. Whelan, J. Ferlay, L. Teppo and D.B. Thomas
2. Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, Kiemeney L, Kriegmair M, Montironi R, Murphy WM, Sesterhenn IA, Tachibana M, Weider J. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005; 66 (Suppl 6A): 4–34.
3. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol* 1998; 22 (12): 1435–48.
4. Mungan NA, Aben KK, Schoenberg MP, Visser O, Coebergh JW, Witjes JA, Kiemeney LA. Gender differences in stage-adjusted bladder cancer survival. *Urology* 2000; 55(6): 876–880.
5. Cantor KP, Lynch CF, and Johnson D. Bladder cancer, parity, and age at first birth. Cancer Causes Control 1992; 3 (1): 57–62.
6. Green A, Beral V, and Moser K. Mortality in women in relation to their childbearing history. *BMJ* 1988; 297(6645): 391-5.
7. Plesko I, Preston-Martin S, Day NE, Tzonou A, Dimitrova E, Somogyi J. Parity and cancer risk in Slovakia. *Int J Cancer* 1985; 36(5):529-33.
8. Reid LM, Leav I, Kwan PW, Russell P, Merk FB. Characterization of a human, sex steroid-responsive transitional cell carcinoma maintained as a tumor line (R198) in athymic nude mice. *Cancer Res* 1984; 44(10):4560-73.
9. Ries LAG, Eisner MP, Kosary CL, *et al,* eds. SEER Cancer Statistics Review, 1975-2002. Bethesda, Md: National Cancer Institute, 2005. Last accessed June 1, 2012. http://www.seer.cancer.gov/csr/1975_2002
10. Schairer C, Hartge P, Hoover RN, Silverman DT. Racial differences in bladder cancer risk a case-control study. *Am J Epidemiol* 1988; 128 (5): 1027–37.
11. Marcus PM, Hayes RB, Vineis P, Garcia-Closas M, Caporaso NE, Autrup H, Branch RA, Brockmöller J, Ishizaki T, Karakaya AE, Ladero JM, Mommsen S, Okkels H, Romkes M, Roots I, Rothman N. Cigarette

smoking, N-acetyltransferase 2 acetylation status, and bladder cancer risk: a case-series meta-analysis of a gene-environment interaction. *Cancer Epidemiol Biomarkers Prev* 2000; 9(5): 461–7.

12. Kiemeney LA and Schoenberg M. Familial transitional cell carcinoma. *J Urol* 1996; 156 (3): 867–72.
13. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first degree relatives of cancer probands. *J Natl Cancer Inst* 1994; 86 (21): 1600–8.
14. Vineis P and Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. *Arch Environ Health* 1991; 46 (1): 6–15.
15. Markowitz SB and Levin K. Continued epidemic of bladder cancer in workers exposed to ortho-toluidine in a chemical factory. *J Occup Environ Med* 2004; 46 (2): 154–160.
16. Kantor AF, Hartge P, Hoover RN, Narayana AS, Sullivan JW, Fraumeni JF. Urinary tract infection and risk of bladder cancer. *Am J Epidemiol* 1984; 119(4):510-5.

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