Clinico-pathological Study of Bladder Cancer in a Tertiary Care Center of South India and Impact of Age, Gender, and Tobacco in Causing Bladder Cancer: A Single Center Experience

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Abstract

Introduction: Bladder cancer (BC) is one of the most common urological malignancies. It is the fourth most common cancer in men and eighth most common malignancy in women of the western world. As per the Indian cancer registry, BC constitutes the ninth most common malignancy and accounts for an overall 3.9% of all cancer cases.

Purpose: The purpose of this manuscript is to do a clinico-pathological study on the BCs and to assess the impact of smoking, age, gender, and adequacy of treatment on the final outcome of the disease.

Materials and Methods: This was a retrospective audit on patients with BCs. All patients with BCs, diagnosed and treated in our institution between 2011 and 2015 were included in our study.

Results: A total of 156 patients were diagnosed and treated over a period of 4½-year from January 2011 to June 2015. Painless total hematuria was the most common presentation seen in 111 patients. BC has been predominantly a disease of elderly age group. High-grade cancers were found predominantly in patients above 60 years of age ($n = 70$), with a $P = 0.04$, while in patients <60 years of age, both high and low-grade cancers were of almost same incidence. The risk of tumor recurrence is considerably less in those who receive adjuvant Bacille Calmette-Guerin or mitomycin C therapy, and the difference between the two groups is statistically significant, with a $P < 0.0001$.

Conclusion: The overall incidence of BC in India is on the rise. Tobacco has been a very strong predisposing factor for BC occurrence. A high index of clinical suspicion, as well as a thorough exploration of all possible epidemiological factors, will help the clinicians and epidemiologists in formulating a definitive disease control program.

Key words: Bacille Calmette-Guerin therapy, Bladder cancer, Hematuria, Smoking, Tobacco, Urothelial malignancy

INTRODUCTION

Bladder cancer (BC) is one of the most common urological malignancies. It is the fourth most common cancer in men and eighth most common malignancy in women of the western world.[1] As per the Indian cancer registry, BC constitutes the ninth most common malignancy and accounts for an overall 3.9% of all cancer cases.[2] With increasing use of tobacco in various forms and with an ever increasing risk of exposure to occupational hazards, more and more of these BCs are being diagnosed nowadays. In spite of various stringent measures taken by various authorities with respect to manufacturing and legislative changes to workplace hygiene, many BCs still do rise through a risk of exposure to occupational carcinogens.[3]

Smoking has been recognized as a very strong independent risk factor for bladder tumor occurrence and recurrence.

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Refraining from smoking for more than 15 years has been identified to reduce the risk of tumor recurrence as well.[4] In general, the risk increases as the frequency and duration of smoking levels increase and the risk typically decreases in former smokers than in current smokers.[5]

Gender has been found to affect the overall survival prognosis of patients with BC. Men have a three-fold greater risk of developing BC than women, but female gender is identified as an independent adverse prognostic factor in terms of both recurrence and progression of the disease. Women with BC are more often diagnosed with a higher tumor stage than men.[6]

Traditionally, BC is usually seen as a disease of advanced age. Nowadays, with an increased use of various diagnostic techniques and increased health awareness among the common public, many new cases of BCs are being diagnosed at a relatively younger age.[7]

Herein, we have analyzed the clinico-pathological characteristics of BC and explored the impact of various factors such as age, gender, and tobacco smoking on tumor characteristics and cellular biology.

MATERIALS AND METHODS

Patient Information
Data of patients with BC, diagnosed and treated in our hospital from January 2011 to June 2015 were traced from our Medical Records Department case files and studied. The available information regarding patients' age, gender, symptoms and mode of presentation, history of tobacco smoking, and use of smokeless tobacco in various forms such as paan masala, tobacco leaves with betel nuts, chewing rolled dried leaves of tobacco were all collected and analyzed.

Treatment Protocol
All patients diagnosed with BC underwent an initial cystoscopic evaluation to identify the type of lesion, its number, and the location. Our hospital being a tertiary referral center, most of the patients already have had an initial urine cytology and cystoscopic evaluation done elsewhere. Transurethral resection of bladder tumor was performed in all patients. Deep muscle biopsy was sent in a separate container, and the uropathologist was requested to specifically look for the presence of detrusor muscle in the specimen and document presence or absence of muscle invasiveness. Those patients, in whom deep muscle invasion could not be commented on, were subjected for re-resection after 3 weeks. Otherwise, re-resection for high-grade non-muscle invasive BCs (HGNMIBC) was not done as a routine. All patients with NMIBC were subjected for adjuvant therapy. 80 mg of intra vesical Bacille Calmette-Guerin (BCG) was our first choice. In those patients who could not tolerate BCG or in whom BCG administration was contraindicated, 40 mg of mitomycin C was administered.

Diagnostic Protocol
All pathological staging and grading were done using the International Society of Urological Pathology classification. Papillary lesions were reported as Ta, non-muscle invasive lesions as T1 and deep detrusor muscle invasive lesions as T2. Grade 1 and 2 were clubbed together as low grade, and Grade 3 lesions were categorized as high-grade lesions. In those specimens where muscle invasiveness could not be commented were subjected for re-resection.

Statistical Analysis
All collected information were analyzed using SPSS software, version 18. The categorical data (variables) such as age, gender, smoking history, smokeless tobacco usage were compared using Chi-square test and Fisher's exact test.

RESULTS

Demographic Incidence
A total of 156 patients were diagnosed and treated over a period of 4½-year from January 2011 to June 2015.

Of these patients, isolated painless total hematuria was the most common presenting symptom, seen in 111 patients. Loin pain associated with hematuria was seen in 18 and irritative urinary symptoms with hematuria in 17 patients. 10 patients had an incidentally detected bladder lesion. Table 1 summarizes the clinical and pathological characteristics of all the 156 patients in our study.

Transitional cell carcinoma (TCC) and its variants constituted the most common histological type, seen in 153 patients (98%). Figure 1 and Table 2 summarizes the spectrum of various histological types noted in our patients.

Impact of Age
BC has been predominantly a disease of elderly age group. The youngest reported patient in our study was 26 years old, who had presented with a solitary polypoidal growth and painless total hematuria, and the oldest reported was an 84-year-old male, with a mean age of 61.5 years and a median age of 60. Figure 2 describes the age distribution of BC in our study. Table 3 describes the age wise pathological distribution of all BCs. High-grade cancers were found predominantly in patients above 60 years of age ($n = 70$), while in patients <60 years of age, both high and low-grade

cancers were of almost same incidence. With regards to the stage of the tumor, T1 tumors accounted for 87% of all BCs.

Table 1: Summary of the clinical and pathological characteristics of all 156 patients in our study

Characteristics	Number (%)
Total number of patients	156
Stage	
T1G1, T1G2	57 (36.6)
T1G3	78 (50)
T2	5 (3.1)
Others**	16 (10.3)
Grade	
Low	57 (36.6)
High	99 (63.4)
Tumor size (cm)	
<3	115 (73.71)
>3	41 (26.28)
Type of growth	
Polypoidal	117 (75)
Sessile	39 (25)
Number of tumors	
Single	121 (77.6)
Multiple	35 (22.4)
Symptoms	
Hematuria alone	111 (71.2)
Irritative symptoms with hematuria	17 (10.9)
Loin pain with hematuria	18 (11.5)
Incidentally detected	10 (6.4)

**Others include squamoid, sarcomatoid, undifferentiated, and glandular variants of TCC, TCC: Transitional cell carcinoma

Table 2: Spectrum of various histological types of bladder cancers observed in our study

Pathology	Number (%)
T1G1, T1G2	57 (36.6)
T1G3	78 (50)
T2	5 (3.2)
Sarcomatoid	2 (1.3)
Squamoid	5 (3.2)
Plasmacytoid	1 (0.6)
Undifferentiated	3 (1.9)
Glandular variant	4 (2.6)
Angiomyxoma	1 (0.6)
Total	156 (100)

Table 3: Impact of age on tumor grade and stage

Characteristics	<60 years	>60 years	P value
Number of patients	55	101	
Smokers	41	70	0.58
Non-smokers	14	31	
Tumor grade (TCC)			
Low (n=57)	26	31	0.039 (without
High (n=99)	29	70	yates correction)
Tumor stage			
T1 (n=135)	46	89	0.08
T2, others (n=21)	3	18	

TCC: Transitional cell carcinoma

Impact of Gender

Table 4 describes the gender wise distribution of BCs. More than 80% of patients were males, with the male to
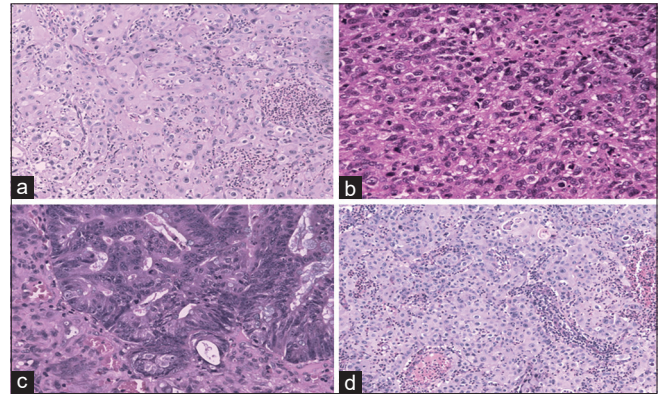

Figure 1: Spectrum of various histological types of TCC bladder. (a) urothelial carcinoma with squamoid differentiation (H and E ×100), (b) urothelial carcinoma with sarcomatoid differentiation (H and E ×100), (c) urothelial carcinoma with glandular differentiation (H and E ×100), (d) high-grade tumor with dense inflammatory response (H and E ×100)
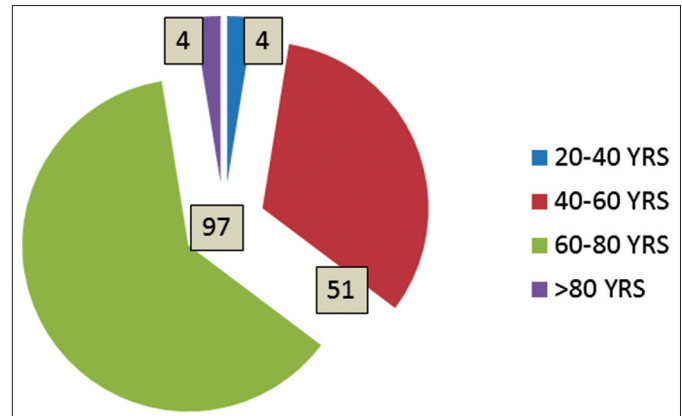

Figure 2: Age distribution of bladder cancer

Table 4: Impact of gender on tumor grade and stage

Characteristics	Male	Female	P value
Number of patients	127	29	
Smokers	109	2	<0.0001
Non-smokers	18	27	
Grade			
Low (n=57)	47	10	0.8346
High (n=99)	80	19	
Stage			
T1	121	14	0.1411
T2 and others	16	5	
Exposure to risk factors			
Tobacco smokers	109	2	
Non-smokers	18	27	
Paan chewers	90	26	
Agricultural pesticides	80	24	

female ratio being 4.4:1. Smoking was the predominant predisposing factor in a majority of males. Only two females gave a history of tobacco smoking. On the other hand, there was a greater incidence of smokeless tobacco usage among the female group, which could have been one of the causative factors for tumor occurrence. Exposure to fertilizers and pesticides were common in both the genders. In such patients, it is evident that either smokeless tobacco or exposure to pesticides and fertilizers may be a stronger predisposing factor, even in those who are never smokers, suggesting that such possible risk factors may be more readily detectable in those unexposed to potent risk factors such as tobacco smoke.

Impact of Treatment

Of the 156 patients, 135 were of NMIBC type. Adjuvant treatment was offered for 125 patients. 10 of them refused any further treatment. Table 5 describes the impact of treatment on the final outcome of the disease. From Table 5, it is well-evident that the risk of tumor recurrence is considerably less in those who receive adjuvant BCG or mitomycin C therapy, and the difference between the two groups is statistically significant, with a $P < 0.0001$. Of the 125 patients, 86 received intra vesical BCG therapy. From the Table 5, Figure 3 gives an overview of the details of treatment given.

Table 5: Impact of adequate treatment on final outcome in T1 patients (*n*=135)

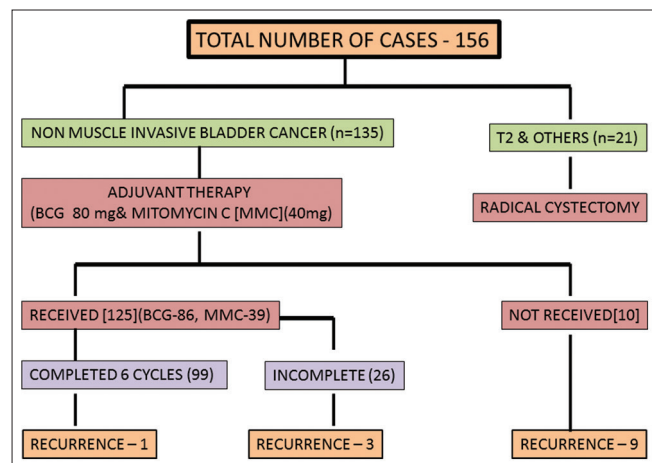| ???	Adjuvant treatment given (6 cycles) (*n*=99)	Adjuvant treatment not given/incomplete [*n*=36 (26+10)]	Two-tailed *P* value
Recurrence	1	12	<0.0001
No recurrence	98	21	
Total	99	36	

Figure 3: An overview of details of treatment given

DISCUSSION

Urothelial cancers account for 5.6% of all male and 1.8% of female cancers in India, with an actual crude rate incidence of about 1 in 174 men and 1 I 561 women.[8]

BC is one of the most common urothelial malignancies. The most common presentation is total painless hematuria, which is seen in more than 90% of all patients with BCs. However, almost all patients will have microscopic hematuria.[9] In our study, 83% of them had painless hematuria as the initial presenting symptom and 93% of them had hematuria at some point of time or the other before a diagnosis is made.

TCC is the most common histological variety, seen in 90% of patients with BC.[10] Various variants of TCC such as squamoid, sarcomatoid, and glandular differentiation are reported, which are very rarely seen. Most of the TCCs are NMIBC and are treated by transurethral resection. More than half of these patients experience recurrence with time.[11]

Furthermore, the epidemiology shows a strong association of BC with various environmental factors such as tobacco smoking, use of smokeless tobacco, exposure to aromatic amines, pesticides, and fertilizers.[12] Furthermore, it exhibits a field change potential, where the entire urothelium is exposed to the effects of such elements with carcinogenic potential.[13]

Cigarette smoking has been a major independent risk factor for BC. Smokers have four-fold increased incidence of developing BC compared to non-smokers.[14] The risk increases as the frequency and duration of smoking levels increase and typically decreases in former smokers compared to current smokers.[15] In our study, overall, 111 patients (71%) were smokers. This less number of overall incidences may probably be due to a majority of female patients being non-smokers. It is also possible that many of the smoking women may not have actually revealed the history of smoking when asked. However, when male patients alone were looked into, 86% of them were found to be chronic smokers.

Tobacco in other forms is also identified to be one of the major predisposing factors. In one of the largest studies conducted by University of Delhi, India, Dwivedhi *et al.*, observed that smokeless tobacco in various forms predisposes to the development of BC.[16] In their study, they observed that paan masala, gutka, khaini or surti, which are various forms of smokeless tobacco, contain procarcinogens such as tobacco, betel

nut, sugar coated fennel, saccharin, and heavy metals such as silver in unknown quantities, which leads to an increased occurrence of BC in this subset of population. Rafique observed that Pakistani women with strong exposure to such smokeless tobacco are more prone to develop BC.[17]

Such BCs usually are of NMIBC type. DeMarco *et al.* observed that at the time of initial diagnosis, 75-85% of all BCs are non-muscle invasive. However, 20-40% of them progress to invasive type within 5 years of primary treatment.[18] This stresses the fact that urothelial malignancies are an ongoing phenomenon, and one needs a more regular and systematic follow-up with appropriate adjuvant therapy.[19]

Optimal treatment of HGNMIBC has always been a challenging task. Such tumors have a variable and unpredictable biological behavior.[20,21] Such patients should be advised to undergo regular adjuvant intravesical BCG therapy and a close follow-up.

Shahin noted that approximately 30% of patients remain recurrence free after BCG therapy, an additional 30% recur after BCG therapy and another 30% progress to muscle invasive stage.[22] Based on such data, some authors have justified the role of radical cystectomy for patients with HGNMIBC.[23]

Limitations

Our study has a few limitations. First of all, it is a study of all patients operated in the last 4½ years, where the follow-up period in a majority of patients is <2 years. There is also a possibility of selection bias, as only patients with documentation of muscle in the specimen were included in our study. The lack of control comparison group also hampers the assessment of the actual efficacy of adjuvant therapy.

CONCLUSION

The overall incidence of BC in India is on the rise. HGNMIBC is a potentially lethal disease. In such cases, transurethral resection alone may not be sufficient, and patients must be subjected for adjuvant therapy and a long-term follow-up. There is a definite male preponderance, owing largely to a greater risk of exposure to risk factors. With advanced age, BCs tend to be of a higher grade with a more lethal outcome. Tobacco in any form has been a very strong predisposing factor for BC occurrence. A high index of clinical suspicion, as well as a thorough exploration of all possible epidemiological factors, will help the clinicians and epidemiologists in formulating a definitive disease control program. Awareness among the public should also be emphasized to make them realize the deleterious consequences of exposure to such risk factors and also to report themselves to the treating physician on the development of any signs and symptoms of BC.

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