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Incidence of Bladder Cancer at a Tertiary Care Centre in North Karnataka

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Abstract

Background: Understanding the prevalence, clinical characteristics, and changing demographics of Indian bladder cancer (BC) has emerged as an important field of study. Herein, we aimed to present the case series of BC patients of a single tertiary care centre in North Karnataka.

Method: This retrospective study was designed for 14 years from 2004 to 2017, conducted in the urology clinic. A total of 468 newly diagnosed BC patients (male = 415; female = 53) were included in the study. Sociodemographic, clinical characteristics, cystoscopic, and pathological findings were recorded and analyzed via IBM SPSS statistics software Inc. version 20.0.

Results: The mean age of the patients was male = 62.27 years and female = 54.22 years. Hematuria was a common clinical symptom in both genders accounting for 42.02 versus 45.28% of the male and female subjects, respectively. Transition cell carcinoma (TCC) was the common variant seen in the male and female participants (92.99 versus 94.88%, respectively). Low-grade cancer was found in patients with >60 years of age in 39.7% versus 42.1% of respectively the males and females (P = 0.002) as compared to the patients <60 years. Non-muscle invasive BC in the males and females was respectively 55.42% versus 52.83%, whereas muscle-invasive cancer was 44.57% versus 47.16% respectively in the two groups (P = 0.008). 53 patients (29.22%) in the both genders received transurethral resection/intravesical Bacilli Calmette-Guerin therapy, which showed a significant improvement (P = 0.019).

Conclusion: Transition cell carcinoma was found to remain the predominant type of BC with painless hematuria in North Karnataka population. This has seriously affected the public health; this trend is expected to be continued due to the high prevalence of smoking. There should be further emphasis on primary prevention of BC by conducting smoking cessation awareness programs.

Keywords: Incidence, Urinary bladder neoplasms, Sociodemographic, Clinical characteristics, Tertiary care centre

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Introduction

The incidence of bladder cancer (BC) appears to be the most prevalent urinary tract malignancy across the world and is rapidly increasing in developing countries.[1] About 2 to 6% of the total malignant tumours are BC, which makes it the fourth most common cancer in males and eighth in females in India.[2] BC is mainly a disease of the aged with more than 70% of the cases occurring at their fifth decade of life, in both men and women.[3] Almost 90% of the bladder tumours are transitional cell carcinoma (TCC). It is three folds more common in men than in women. Age, gender, occupation, and racial and environmental factors affect the survival and prognosis of patients with BC.[4] At least 75 to 80% of the newly diagnosed BC is superficial and non-invasive papillary TCC. Additionally, at least 50 to 75% of these patients will recur over time.[5] This high recurrence rate highly impacts the prevalence rates, making BC the second most common cancer after prostate cancer in males.[6] This necessitates long-term surveillance over decades, providing the possibility of multiple hospital treatments. To the best of our knowledge, no large case series have been presented to describe the demographic data of bladder cancer from North Karnataka. On account of the significant impact of bladder cancer on healthcare burden and the need for frequent and long-term cystoscopic examination, we conducted the present study to investigate the clinical characteristics of bladder cancer correlated with age, gender, grade, and stage on the biology of cancer.

Patients and Methods

The KLES Kidney Foundation Institutional Ethics Committee approved this retrospective study under the ethics code of KLESKF/IEC/2015/23. The informed consent was obtained from all the patients. The medical records of the patients with cystoscopy and histopathological confirmed that bladder cancer cases were traced through the database. The data from January 2004 to June 2017 were reviewed and the total number of subjects was 468. The data acquisition and interpretation of cases were done by experts and chief urologists. All the details of the patients from the epidemiological point of view, symptoms, signs, radiological, endoscopic, histopathological features, various treatment modalities offered, and the follow-up of patients were studied. The variables analyzed in detail were as follows: sociodemographic features, including the patients' age, occupation, residential, and addiction; basic clinical features, includes symptomatology, comorbidities, medical history, and family history of bladder cancer; clinical characteristics, namely computed tomography (CT) scans of the bladder, pelvic, and abdomen in the majority of the cases. Bone scan and magnetic resonance imaging (MRI) were carried out as per clinical indication for diagnostic and staging purposes. Since it was a single-center study in the southern part of India, we carefully looked into the determinants of the bladder cancer risk and evaluated the variables related to sociodemographic features, clinical characteristics, and cystoscopic and pathological findings. The variables were recorded and analyzed using IBM SPSS statistics via software Inc. version 20.0.

Diagnostic protocol

The entire pathological staging and grading was done following the International Society of Urological Pathology classification. Papillary lesions were reported as Ta, non-muscle-invasive lesions (NMIBC) (as T1), and 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. The specimens in which muscle invasiveness could not be commented were subjected for re-transurethral resection of bladder tumour.

Treatment protocol

The patients diagnosed with BC underwent a standard procedure of cystoscopic evaluation to identify the type of lesion, its number, and location. Transurethral resection of bladder tumour was performed in all the patients. All the participants with NMIBC were subjected to adjuvant therapy. 80 mg of Intra vesicle Bacillus Calmette-Guerin (BCG) was the first choice. In the patients who could not tolerate BCG or in whom BCG administration was contraindicated, 40 mg of

Table 1. Bladder cancer incidence rates recorded in districts of North Karnataka, Goa, and Maharashtra with respect to gender and age

Place of Residence	Male		Female		Total		Year-wise cases recorded		
	n	%	n	%	n	%			
Belagavi	122	29.39	12	2.26	134	28.63	Year	Frequency	Percentage
Dharwad	37	8.91	8	15.09	45	9.62	2004	24	5.13
Hubli	23	5.54	6	11.32	29	6.20	2005	26	5.56
Chikodi	45	10.8	9	16.98	54	11.54	2006	23	4.91
Bagalkot	32	7.71	5	9.43	37	7.91	2007	37	7.91
Vijayapur	16	3.85	4	7.54	20	4.27	2008	38	8.12
Gadag	20	4.81	3	5.66	23	4.91	2009	27	5.77
Uttar Kannada	24	5.78	3	5.66	27	5.77	2010	21	4.49
Haveri	9	2.16	0	-	9	1.92	2011	34	7.26
Davengere	13	3.13	0	-	13	2.78	2012	39	8.33
Gulbarga	10	2.40	0	-	10	2.14	2013	59	12.61
Goa	20	4.81	2	3.77	22	4.70	2014	54	11.54
Miraj	15	3.61	0	-	15	3.21	2015	36	7.69
Kolhapur	18	4.33	1	1.88	19	4.06	2016	34	7.26
Raichur	11	2.65	0	2.26	11	2.35	2017	16	3.42
Total	415	100.00	53	79.66	468	100.00	Total	468	100.00

Mitomycin C was administered.

Results

Bladder cancer incidence

A total of 468 patients were diagnosed with BC during the period of 2004 to 2017, among whom there were 415 male subjects (88.67%) and 53 female subjects (11.04%). Table 1 represents the distribution of BC incidence year-wise and with respect to gender and place of residence.

Sociodemographic features

The mean age of male patients at the time of diagnosis (n = 415) was 62.27 ± 11.90 years (ranging from 30 to 90 years) and that of female patients (n = 53) was 54.22 ± 16.24 years (ranging 30 to 90 years); the majority of the patients were older than 50 years old. Only 6.62% (n = 31 out of 468) of the patients presented with bladder cancer at an age of younger than 40, while only 0.64% (n = 3; 1 = male and 2 = female) of them presented with less than 30 years of age. Figure 1 depicts the age-wise pathological distribution of bladder tumours. In the 468 cases, the total occupation status of blue-collar was (n = 292) 62.39%, among which (n = 273) 93.49% were male and (n = 19) 6.51% were female. White-collar was (n = 154) 32.91%, out of which (n = 140) 90.91% were male and (n = 14) 9.09% were female; homemaker was (n = 22) 4.70%, out of which (n = 2) 9.09% were male and (n = 20) 90.91% were female.

Basic clinical features

Family history in male patients was (n = 26) 6.26% and in female subjects (n = 3), it was 5.66%; on the contrary, (n = 416) 88.9% had no family history. However, the data for family history was missing in (n = 23) 4.91% of the patients. Bothersome symptoms revealed that hematuria was the most common clinical presentation encountered in both age groups (42.02 versus 45.28%). The other participants presented with lower urinary tract symptoms (88.68 versus 22.65%). Abdominal pain (7.05%) showed statistical significance in both groups ($P = 0.015$), dysuria was found in 2.61% of the cases ($P = 0.106$), and burning micturition was 7.51% with statistical significance ($P = 0.006$). The remaining patients had hesitancy (1.07%), urgency (6.62%), nocturia (9.19%), dribbling (1.92%), poor urinary stream (9.4%), retention (2.35%), intermittency (3.63%), loss of appetite (1.28%), and incontinence urge (2.78%) in both male and female patients. Nearly 55.42% of the patients (male and female) had concomitant diseases and 44.57% presented no comorbidity. The correlation of comorbidities showed no significance in male and female groups ($P = 0.213$), which is illustrated in table 2.

Clinical characteristics

The pathological findings revealed that TCC was the most common variant in 92.99% (n=199) of the cases with <60 years of age and 94.88% (n = 241) of the cases with >60 years of age,

Table 2. History of comorbidities associated with bladder cancer

Comorbidities	Male n (%)	Female n (%)	*P*-value
Diabetes	47 (11.3)	3 (5.6)	0.0213*
Hypertension	41 (9.8)	8 (15.0)	
Asthma	2 (0.4)	1 (1.8)	
Renal failure	3 (0.7)	5 (9.4)	
Bladder stones	7 (1.6)	6 (11.3)	
COPD	7 (1.6)	-	
Tuberculosis	8 (1.9)	-	
Urinary tract infections	22 (5.3)	-	
Neurogenic bladder	3 (0.7)	-	
Parkinson	1 (0.2)	-	
Other complications	89 (21.4)	3 (5.6)	
No comorbidity	185 (44.5)	27 (50.9)	

*$P < 0.05$; COPD: Chronic obstructive pulmonary disease; Other complications: Cerebrovascular accident, Hyperthyroidism, Hypothyroidism, Thrombocytopenia, Balanitis Xerotica Obliterans, Ischemia Heart Disease.

including both male and female subjects. Only 3.27% (n=7) had squamous cell carcinoma (SCC) in those with <60 years of age and 1.96% (n = 5) in those with >60 years of age. Adenocarcinoma was observed only in eight patients (3.37%) in the group with <60 years of age and 3.16% (8) in the group with >60 years of age. Table 3 demonstrates the correlation among age, addiction (smoking, alcohol, and tobacco), tumour histology, and tumour grade and stage. Low-grade cancer was found to be more prevalent in patients older than 60 years (39.7% versus 42.1%) ($P = 0.002$) compared with those younger than this age. A total of 30.1% (n=125) of the males and 33.9% (n=18) of the females with bladder cancer smoked or had an intake of tobacco in some form ($P = 0.021$). The incidence of various cancer stages and grades was statistically significant ($P = 0.008$) in both groups. 29 (6.9%) male patients and two (3.7%) female cases had muscle-invasive disease at the time of presentation. Table 4 exhibits the pathological distribution of bladder cancer in males and female.

Treatment

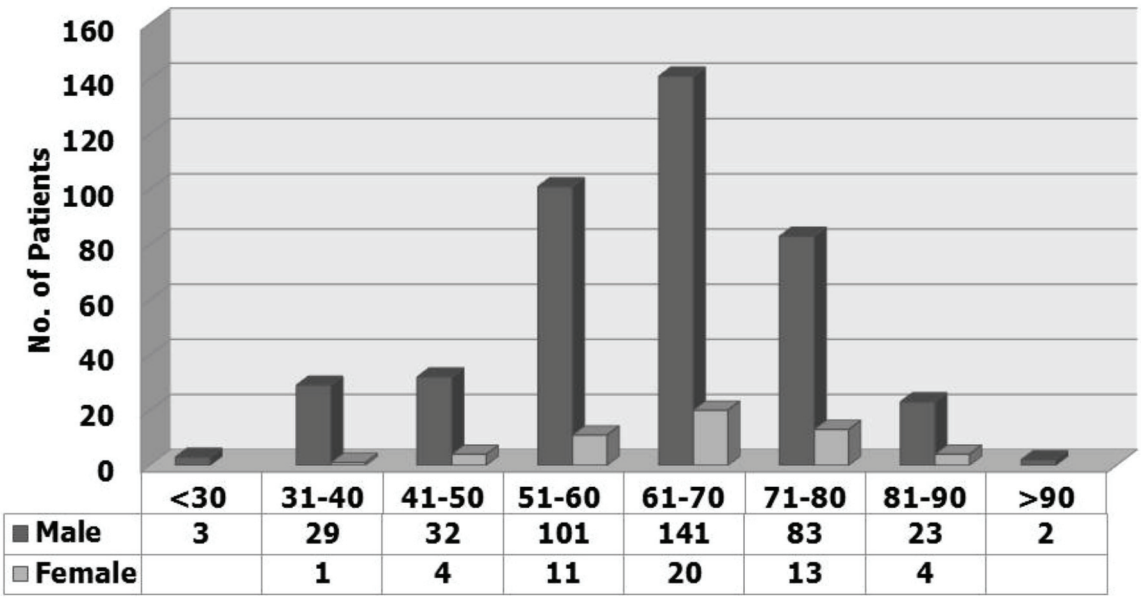

Figure 1. The figure represents the distribution of bladder cancer patients with age group and gender. Several patients were categorized in the age group of between 51 to 60 and 61 to 70.

Table 3. Correlation of age on addiction, tumour histology, tumour grade, and stage

Characteristics	<60 years (%)	>60 years (%)	*P*-value
Number of Patients	214 (45.7)	254 (54.2)	
Addiction			
Smoking	63 (29.3)	79 (31.2)	0.3268
Alcohol	16 (7.4)	24 (9.4)	
Tobacco	33 (15.3)	65 (25.9)	
Smoking and tobacco	13 (6.1)	11 (4.3)	
Alcohol and tobacco	20 (9.3)	10 (3.9)	
Smoking and alcohol	40 (18.6)	22 (8.6)	
No addiction	29 (13.4)	42 (16.6)	
Data missing	01 (0.4)		
Tumour histology			
Transition cell carcinoma	199 (92.9)	241 (94.8)	0.2398
Squamous cell carcinoma	7 (3.2)	5 (1.9)	
Adenocarcinoma	8 (3.7)	8 (3.1)	
Grade			
Low	85 (39.7)	107 (42.1)	0.0024*
High	129 (60.2)	147 (57.8)	
Stage			
Non-muscle invasive (Ta+T1)	74 (34.5)	105 (41.3)	0.0218
Ta	46 (21.4)	34 (13.3)	
T1	82 (38.3)	97 (38.1)	
Invasive (T2)	12 (5.6)	18 (7.1)	

*$P<0.05$

Most of the patients 54.71% (n = 256) underwent TURBT as a definitive treatment in both groups whereas cystoscopy/biopsy was 4.8% (n = 22) and only 28 (5.89%) patients underwent radical cystectomy that had muscle-invasive (Table 5). 53 (29.22%) in both groups received intravesical BCG therapy, which showed a significant improvement (P = 0.018) and none of them had recurrence during the follow-up period.

Discussion

The present study revealed that the majority of the cases (male and female) were in the age group ranging from 50 to 70 years older. The overall mean age of the male patients (n = 415) was 62.27 ± 11.90 years (ranging from 30 to 90 years) and that of the female patients (n = 53) was 54.22 ± 16.24 years (ranging from 30 to 90 years). In this study, only 6.62% (n = 31 out of 468) of the patients presented with bladder cancer among those with the age of less than 40, while only a few patients 0.64% (n = 3; 1 = male and 2 = female) were lower than 30 years old. The results of the present study were compatible with the well-known characteristics of the disease, which frequently affect the elderly population of both genders.[7-9]

Familial BC is rare compared with the familial occurrence of cancer in other tumour sites.[10, 11] However, there appears an increased risk of BC in individuals with a family history of cancer, particularly in those with first-degree relatives, who developed BC at the age 40 or earlier.[12, 13] Herein, we observed identification of positive family history for BC in first-degree relatives to be in 6.26% of the male (n = 26) and 5.66% of the female (n = 3) cases; on the contrary, 88.9% (n = 416) had no family history. However, there were not enough data available regarding family history in 4.91% (n = 23) of the patients. This is in line with previous studies, indicating that there is twice higher risk in first-degree relatives of BC patients.[14] Inherited genetic factors, such as the genetic slow acetylator N-acetyltransferase 2 (NAT2) variants and glutathione S-transferase mu 1 (GSTM1)-null genotypes, have been established as risk factors for BC.[15, 16] In the

Table 4. Correlation of gender on addiction, tumour grade, and stage

Characteristics	Male n (%)	Female n (%)	*P*-value
Number of Patients	415	53	
Addiction			
Smoking	125 (30.1)	18 (33.9)	0.0212*
Alcohol	37 (8.9)	3 (5.6)	
Tobacco	83 (20.0)	15 (28.3)	
Smoking and tobacco	22 (5.3)	1 (1.8)	
Alcohol and tobacco	30 (7.2)		
Smoking and alcohol	59 (14.2)	3 (5.6)	
No addiction	58 (14.0)	13 (24.5)	
Data missing	1 (0.24)		
Grade			
Low	165 (39.7)	28 (52.8)	0.0510*
High	250 (60.2)	25 (47.1)	
Stage			
Non-muscle invasive (Ta+T1)	155 (37.3)	23 (43.3)	0.0084*
Ta	75 (18.0)	5 (9.4)	
T1	156 (37.5)	23 (43.3)	
Invasive (T2)	29 (6.9)	2 (3.7)	

*$P<0.05$

current research, evidence of family history in cases with BC suggested a significant influence of genetic predisposition on its incidence, especially via the impact on susceptibility of other risk factors.

Bladder cancer presented with painless hematuria in 42.02 versus 45.28% of the male and female patients, respectively. Nonetheless, in reality, nearly all patients with cystoscopically detectable BC have at least micro-hematuria, if enough urine samples are tested. In our study, 90% of the male patients presented with painless hematuria compared with 10% of the women, as the initial symptom, and 51.28% of them had hematuria at some point of time or the other before diagnosis was made. This high incidence may be due to the lack of screening for microscopic hematuria in the form of dipstick or flexible cystoscopy, even in high-volume centres.[17]

TCC was the most common primary pathologic subtype of BC, observed in >90% of bladder tumour in the literature.[18] A considerable variability has been noted in the prevalence of SCC of bladder in different parts of the world. SCC and adenocarcinoma are less common and have been reported to occur in approximately 5% in the United Kingdom and 7% in the United States.[19] In certain regions of the world, mainly Europe and Egypt, where schistosomiasis (also known as bilharziasis) infection is endemic, the prevalence of SCC accounts for 75% of bladder tumour.[20] In our study, 92.99% (n = 199) of the patients aged <60 years and 94.88% (n = 241) of those aged >60 years had TCC in both genders. SCC was observed in both genders with only 3.27% (n = 7) in the subjects aged <60 years and 1.96% (n = 5) in those aged >60 years. Adenocarcinoma was observed to be 3.37% (n = 8) in the cases with <60 years of age and 3.16% (n = 8) in those with >60 years of age in both male and female patients.

According to the literature, smoking is considered as a major risk factor, accounting for 50% of the bladder tumours.[21] There is a direct pathophysiologic link between tobacco and BC as tobacco smoke contains aromatic amines, such as b-naphthylamine and polycyclic aromatic hydrocarbons, known to cause BC.[22] Tobacco consumption (smoking and smokeless tobacco) is common in the Indian population in both genders; thus, its epidemiologic impact is massive. In our study 8.55% (n = 40 of 415 male) were smokers, regardless of age; however, no female smokers were reported during the study. In

Table 5. Treatment of bladder cancer provided

Treatment	Male n (%)	Female n (%)	*P*-value
TURBT	189 (52.79)	67 (60.9)	0.0185*
Cystoscopy and biopsy	13 (3.63)	9 (8.18)	
Radical cystectomy	21 (5.86)	7 (6.36)	
TURBT and intravesical BCG therapy	43 (12.01)	10 (9.09)	
Chemotherapy	10 (2.79)	2 (1.81)	
Radiotherapy	8 (2.23)	1 (0.9)	
Chemotherapy and radiation	12 (3.35)	3 (2.72)	
Cystectomy and chemotherapy	9 (2.51)	2 (1.81)	
Patient refusal for treatment	53 (14.80)	9 (8.18)	

*$P<0.05$, TURBT: Transurethral resection of bladder tumour; BCG: Bacillus Calmette-Guerin

addition, alcohol consumption was noted in the males to be 73.47% (n = 72), which was 20.94% in the females (n = 26). Smokeless tobacco was a common intake in the male cases (71.83%, n = 51), which was found to be far less in the female cases (28.17%, n = 20). We observed a heavy consumption of smokeless tobacco in both genders because several patients' occupation was laborer's in tobacco-making industry situated around 90 km away from our tertiary care center. Thus, environmental exposure to tobacco smoke has also been suspected as a risk factor of BC.[23] A large analysis found environmental exposure to be significantly related to BC incidence in women exposed to cigarette smoke during childhood and adulthood. We also noticed that several patients had multiple habits, like smoking and smokeless tobacco, which was 95.80% in the males (n = 137) and 4.20% in the females (n = 6). Alcohol and tobacco were noticed only in males (5.13%, n = 24). Smoking and alcohol were reported in 96.67% of the males (n = 29) and 3.33% of the females (n = 1). However, 13.25% of the patients had no addiction to any of the above-mentioned risk factors. Meanwhile, in our study, the incidence of smoking or smokeless tobacco in any forms was much higher in males compared with that in females and those aged below 60.

Following smoking, occupational exposure to urothelial carcinogens is the second most important risk factor accounting for 5 to 20% of all bladder cancers. The relative risk of occupational exposure to carcinogens is likely underestimated and varies from country to country. Current or historical exposure to carcinogens, namely aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons, have been viewed as the vital risk factor for BC. Roughly 20% of all BCs have been suggested to be related to such exposure, mainly in industrial areas processing paint, dye, metal, and petroleum products. Herein, a total of 62.39% (n = 292) of the patients had blue-collar occupation, followed by white-collar 32.91% (n = 154) and homemaker 4.70% (n = 22) occupations.

In this study, we found 42.1% low-grade cases (n=107) in the patients aged >60 years older during the time of presentation, whereas taking gender into account, it was 39.7% (n = 165) in males and 52.8% (n = 28) in females. Similarly, high-grade tumour was found to be more prevalent in the males (60.2%, n = 250), which was 47.1% in the females (n = 25). Our results are in concordance with those of previous studies, suggesting that younger patients frequently present with low-grade and lower stage tumours than their elder counterparts.[22] This is on the contrary to the common belief that the behaviour of cancer is more aggressive in younger age groups.[23] On the other hand, it has been witnessed that genetic variations recurrently seen in older adults are extremely rare in young patients.[23] In our study, only a few patients had low/high-grade tumour in the younger age group with statistical significance ($P = 0.002$). Moreover, pathological staging showed non-muscle-invasive bladder cancer in the male subjects (55.42%, n = 230), which was 52.83% in the females (n = 28).

Furthermore, muscle-invasive carcinoma was observed to be 44.57% (n = 185) in the males and 47.16% (n = 25) in the females, which showed statistical significance ($P = 0.008$) in comparison with both genders regardless of age. Compared with the data available from the west, a disproportionate decrease in tumour incidences in females could be due to less exposure to carcinogenic elements since a lower number of women work outside in India. Additionally, females tend to present to the hospital less because of several social/psychological reasons.

The optimal treatment of non-muscle invasive bladder cancer has always been challenging. Such tumours have a variable and unpredictable biological behaviour.[24] Transurethral resection of bladder tumours and intravesical BCG therapy are the mainstay of treatment for superficial urothelial carcinoma. Partial/radical cystectomy is considered as a treatment of choice for muscle invasive bladder carcinoma.[25] In our study, most of the patients underwent TURBT/BCG, as the first-line treatment in 31.3% of the males (n = 130) and 33.9% of the females (n = 18). Such patients were advised to undergo regular adjuvant intravesical BCG therapy and a close follow-up. Partial cystectomy was performed for the patients with muscle-invasive (n = 120) 28.9% (males) and (n = 9) 16.9% (females) only (n = 13) 8.06% underwent radical cystectomy, which was statistically significant ($P = 0.019$) in the both groups. The other patients opted for chemotherapy or radiotherapy depending upon the tumour progression. However, 19.3% (n = 46) of them from both genders refused to undergo treatment due to lack of financial assistant and poor physical fitness. All the patients who underwent treatment were doing well in a median follow-up of nine months although the follow-up period was short to comment on prognosis after TURBT/BCG and partial/radical cystectomy. Nevertheless, in the current paper, we did not investigate bias whereas several epidemiological studies have reported that bias may lead to overestimation in previously reported increased risks of bladder cancer associated with type 2 diabetes.[26]

Conclusion

The outcomes of our study revealed that bladder cancer remains a heterogeneous disease with heterogeneous outcomes. The incidence of bladder cancer is growing in North Karnataka, southern India. It is also on an increasing trend in developing countries across the world. Although stage and grade offer considerable predictive discrimination, the addition of other clinicopathological parameters may improve the ability to individualize bladder cancer management. The predominant risk factors in our subjects included tobacco smoking, occupational chemical exposure, and environmental toxins. The majority of prediction tools for bladder cancer focus on the prediction of disease recurrence and progression in non–muscle-invasive bladder cancer or disease recurrence and survival following radical cystectomy. Most of the patients were of the age group over 50 years and cigarette smokers, which accounted for 50 to 65% of all the cases. Other environmental risks are believed to be largely related to occupational exposures to carcinogenic compounds (aromatic amines), which increases the risk by 20%.

Conflict of Interest

None declared.

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