



A Clinicopathological Correlation of Bladder Cancer in Young and Old Patients: Our Experience and Review of Literature

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Abstract

To compare the clinical, cystoscopic, and pathological characteristics of bladder cancer in patients younger than 40 years of age and those of patients older than 40 years of age.

We conducted a prospective observational study at our department from September 2019 to February 2021 to compare the clinico-pathological characteristics of young and old patients with biopsy proven bladder cancer after a transurethral resection of bladder tumour. The patients were managed according to standard guidelines.

Two hundred sixty-eight patients of bladder cancer were included in the analysis. Out of these, 58 patients were < 40 years of age and 210 were > 40 years. The mean age of two groups were 31.43 ± 6.30 vs 59.08 ± 9.87 years. With respect to tumour grade, 36.2% (versus 17.6%) of young patients had low grade tumour, and 58.6% had high-grade tumour (versus 82.4%). In the young population, 63.8% patients had NMIBC (versus 61.9%) and 36.2% had MIBC (versus 38.1%). Even in the NMIBC group, a large majority of young patients had high-risk disease (51.4%).

The incidence of bladder cancer is on the rise in the northern belt of India, especially in the younger age group. High exposure to smoke and heavy metals in drinking water/occupation are the major risk factors. Majority of young patients aged < 40 years had a high-grade disease on presentation and a large subset had muscle invasive bladder cancer, contrary to previously reported studies.

Keywords Bladder cancer · Young patients · < 40 years · Urothelial carcinoma

Main points

1. The incidence of bladder cancer is on the rise in the northern belt of India along the gangetic plains, especially in the younger age group.
2. High exposure to smoke via smoking/burning firewood and exposure to heavy metals through drinking water or occupation are the major risk factors.
3. The results of our study have shown that bladder cancer in younger population less than 40 years of age is an aggressive tumour with almost 60% of the patients having a high-grade disease, 36.2% patients had a muscle invasive bladder cancer.
4. Out of the 63.8% patients with a non-muscle invasive cancer, 51.4% had a high risk on stratification. Also, 7 patients (12.1%) had a metastatic disease out of which 6 are receiving palliative chemotherapy and one expired. Thus, this study clearly highlights the aggressive and lethal behaviour of the disease even in younger population.
5. More randomised prospective studies are required to clearly elucidate the clinicopathologic biology in this age group for the early identification and management of the patients with worse prognosis.

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Introduction

Bladder cancer is amongst the most common malignancies of the urinary tract. It ranks ninth among the most commonly diagnosed cancers worldwide [1]. Every year, more than 380,000 new cases are diagnosed and about 150,000 deaths are caused by this dreaded disease [1]. At any given point in time, about 2.7 million people have a history of being diagnosed with bladder cancer [2]. As far as the Indian scenario goes, it is the ninth most commonly occurring cancer accounting for 3.9% of all cancer cases [3]. The median age at diagnosis is 69 years of males and 71 years for females [4]. Though the male: female ratio is 3.8:1, females present with more advanced form of disease and have worse outcomes as compared to males [4]. The most common histological type of bladder cancer is urothelial carcinoma accounting for 90% of cases. Less common types include squamous cell carcinoma, adenocarcinoma and small cell carcinoma.

Patients who have gross hematuria have bladder cancer rates of about 13 to 35% and those with microscopic hematuria have rates of about 0.5 to 10.5% [5]. At the time of diagnosis, about 70 to 85% of TCC's are superficial [stages Ta, T1, carcinoma in situ (CIS)] and are collectively termed as non-muscle invasive bladder cancer (NMIBC). Approximately 15–30% invade the deep muscle (T2, T3, T4) and are termed as muscle invasive bladder cancer (MIBC). Among patients who undergo radical cystectomy for MIBC, 57% already have muscle invasive at presentation, while 43% initially diagnosed as NMIBC later progressed to involve the muscle despite organ-preserving treatment [6]. Almost one fourth of patients undergoing radical cystectomy have lymph nodes involved at the time of surgery and almost a third have undetected metastases at the time the primary tumour is being treated [7].

Urothelial carcinoma of the bladder is a disease of the middle aged and the elderly. The incidence of urothelial carcinoma of the urinary bladder in young patients is rare with 0.4 to 1% of bladder tumours presenting in the first four decades of life [8]. Due to its rarity, the natural history and prognosis of bladder cancer in young adults is not well elucidated. Some studies have reported similar prognosis in young age group as compared to the elderly, whereas many have also reported decreased progression and recurrence rates in the young population and hence better prognosis. It also remains unclear whether this better prognosis is due to lower stage and grade of the disease in the young population or is it due to the indolent nature of the disease in this age group. The young population with bladder cancer represents a heterogeneous group with most of the cases having either similar or low stage and grade as compared to the older population. However, previous studies on the topic also indicate a small subset of patients in this group who have a more aggressive form of disease with higher stage and grade, and also a higher percentage of variant histology.

A long debated question is whether the age at diagnosis of bladder cancer has any prognostic significance or not [9]. Thus, this study is aimed at studying the clinical and pathological characteristics of bladder cancer in patients younger than 40 years of age as compared to those more than 40 years of age. The reason for choosing 40 years as a cut-off is due to the following two reasons [10]. Firstly, it has been shown in several studies that the epidemiological data changed gradually from 30 to 40 years and then from 40 to 50 years. Also, the incidence rates gradually increase with age. The incidence rates in > 70 years is 2 to 3 times more than those aged 55–69 and 15 to 20 times more than those aged between 30 and 50.

Methods

We conducted a prospective observational study at our department from September 2019 to February 2021 to compare the clinical, cystoscopic, and pathological characteristics of

bladder cancer in patients younger than 40 years of age and those of patients older than 40 years of age. The study was designed to conform to the Declaration of Helsinki and ICMR guidelines for ethical biomedical research on human subjects. Following Institutional Ethics Committee approval (AIIMS/IEC/19/1012), a patient information document was presented to each patient fulfilling the above mentioned criteria. After explaining pertinent details of the study, a valid informed consent was obtained for assessment according to a pre-designed pre-tested proforma. The authors confirm the availability of, and access to, all original data reported in this study.

The primary objective was to evaluate the clinical, cystoscopic and pathological characteristics of bladder cancer in the two groups. All patients (any age and sex) with biopsy proven urinary bladder cancer, new or follow-up willing to give informed consent were included in the study. Patients who had received previous pelvic radiotherapy/chemotherapy and who had a benign lesion on histopathology were excluded from the study.

During recruitment, demographic and patient data was recorded including medical history, physical examination and the required laboratory and radiological investigations. After a detailed pre anesthetic check-up and clearance for surgery, a primary TURBT (Transurethral resection of bladder tumour) was performed in every patient and the intra-operative findings documented on a bladder map. TURBT specimen and deep muscle was sent for histopathological examination in formalin. Intra-operative cystoscopic findings were recorded as follows:

1. Size of the tumour (< 3 cm/> 3 cm)
2. Solid/papillary
3. Sessile/pedunculated
4. Single/multiple

The histopathology of all TURBT specimen was reported according to the 2004 WHO/ISUP (fourth edition) classification of tumours of urinary system by an expert pathologist including presence or absence of deep muscle and its involvement by tumour. The following pathological factors were noted.

1. Tumour stage (Ta/T1/> T2).
2. Tumour grade (high grade/low grade).
3. Carcinoma in situ (CIS; present/absent).
4. Deep muscle in specimen (present/absent and its involvement if present).
5. Histological variant of bladder tumour.

After a histopathological diagnosis, radiographic extent of tumour and a detailed metastatic work up, the tumour was staged and managed according to institution protocol following standard guidelines.

Discrete categorical data was described in terms of frequency and proportion. Continuous variables were described either as mean \pm standard deviation or in the form of median and interquartile range as per the requirement. We compared proportions and odds ratio for categorical data using chi-square test and Fisher's exact test as and when required. The means were compared using Student's *t* test and Mann–Whitney *U* test as applicable. All the statistical tests were performed with a significance level of $\alpha=0.05$ (95% C.I) and analysis was conducted using statistics software SPSS version 23.0 (IBM SPSS Inc., NY, USA).

Results

A total 325 patients with bladder mass were screened for study. Out of these, 57 patients were excluded from the study. Fifty-one patients denied consent and six patients had benign disease. Remaining 268 patients with diagnosed bladder cancer on histopathology were included in the analysis. Out of these, 58 patients were equal to or younger than 40 years of age and 210 were older than 40 years of age.

The mean age of young patients was 31.43 ± 6.30 years and that of the older population was 59.08 ± 9.87 years. There was no significant difference between the various groups in terms of distribution of gender and geographical location. The presenting complaints and the risk factors are presented in Table 1. In the current study, 60.3% of the participants in the group ≤ 40 years were exposed to tobacco as compared to 75.2% of the participants > 40 years. Twenty nine percent of the participants in the group ≤ 40 years had occupational exposure to chemicals as compared to 43.8% of the older participants. The most common presenting complaint was hematuria seen in 91.4% of young patients and 88.1% of older patients. Other significant presenting complaints included suprapubic pain, LUTS, and dysuria. There was no statistical difference in the mean hemoglobin and serum creatinine of participants in the two groups on presentation (Table 1).

There was no significant difference between the various groups in terms of distribution of number of tumours on imaging and hydronephrosis. The mean (SD) tumour size (cm) in the ≤ 40 years group was 4.31 (2.31). The mean (SD) tumour size (cm) in the > 40 years group was 2.78 (2.13). Also, there was no statistical significant difference in the distribution of T, N and M stages in the two groups. The tumour characteristics on imaging and the clinical TNM staging is described in Table 2.

Morphologically on endoscopy, 46.6% of the participants in the group ≤ 40 years (versus 38.6% in > 40 years) had solid tumours and 53.4% of the participants in the group ≤ 40 years (versus 61.4% in > 40 years group) had papillary tumours. 53.4% of the tumours in the group ≤ 40 years

(versus 45.2% in > 40 years group) were sessile and 46.6% of the tumours in the group ≤ 40 years (versus 54.8% in > 40 years group) were pedunculated. There was no statistically significant difference in the distribution of tumour size, number and morphology on cystoscopy between the two groups (Table 2).

On histopathology, 22.4% (versus 4.3%) of the participants in the group ≤ 40 years had tumour stage pTa, 41.4% of the participants in the ≤ 40 years had tumour stage pT1 (versus 57.6%) and 36.2% of the participants in the group ≤ 40 years had tumour stage pT2 (versus 38.2%). With respect to tumour grade, 36.2% (versus 17.6%) of the participants in the group ≤ 40 years had low grade tumour, 58.6% of the participants in the group ≤ 40 years had high-grade tumour (versus 82.4%) and 5.2% (versus 0%) of the participants in the group ≤ 40 years had PUN-LMP tumour. In the current study, 36.2% of the participants in the group ≤ 40 years were muscle invasive as compared to 38.1% of the participants in the group > 40 years. The distribution of histological variants of tumours are presented in Table 3. In the current study, amongst participants ≤ 40 years with NMIBC, 29.7% of the participants had low-risk disease (versus 0.8%), 18.9% of the participants had intermediate risk (versus 0%) and 51.4% (versus 99.2%) of the participants had high-risk disease (Table 3). Amongst participants ≤ 40 years, 41.4% of the participants in the group received BCG (versus 57.6%), 19.0% of the participants were on active surveillance (versus 0.5%), 1.7% of the participants were on bladder preservation protocol, 10.3% (versus 19%) of the participants underwent RC (with/without NACT), 5.2% of the participants received NACT (versus 5.2% in > 40 years), 10.3% of the participants received palliative chemotherapy (versus 12.4%), 6.9% of the participants expired (versus 3.3%) and 5.2% of the participants (versus 1.9%) were lost to follow-up (Table 3).

Discussion

Bladder cancer in young adults is rare and all the epidemiological studies so far support a “low grade- low stage” cancer distribution in this age group. However, the results of the current study are in contradiction to this and may signal a recent trend change in the epidemiological distribution of bladder cancer in this age group. The incidence of this lethal disease occurring in patients younger than 40 years of age is around 0.4 to 1%. At our centre, which caters to the population mostly comprising of the states of Uttarakhand and western Uttar Pradesh, out of a total of 325 patients of bladder cancer treated from a period of September 2019 to February 2021, 58 patients were younger than 40 years of age (17.8%).

Table 1 Socio-demographic characteristics, presenting complaints and risk factors of study participants

Parameters	Age group		<i>p</i> value
	≤ 40years (<i>n</i> = 58)	> 40years (<i>n</i> = 210)	
Mean age (years)	31.43 ± 6.30	59.08 ± 9.87	0.535
Gender			0.127
Male	48 (82.8%)	189 (90.0%)	
Female	10 (17.2%)	21 (10.0%)	
Address			0.737
Uttarakhand	34 (58.6%)	121 (57.6%)	
Uttar Pradesh	24 (41.4%)	84 (40.0%)	
Others	0 (0.0%)	5 (2.4%)	
Occupation			< 0.001
Farmer	11 (19.0%)	61 (29.0%)	
Factory worker	11 (19.0%)	38 (18.1%)	
Self-employed	5 (8.6%)	37 (17.6%)	
Laborer	14 (24.1%)	15 (7.1%)	
Homemaker	6 (10.3%)	22 (10.5%)	
None	0 (0.0%)	19 (9.0%)	
Professional	0 (0.0%)	14 (6.7%)	
Student	9 (15.5%)	0 (0.0%)	
Cook	2 (3.4%)	4 (1.9%)	
Duration (months)	7.72 ± 12.21	5.17 ± 6.01	0.483
Hematuria (present)	53 (91.4%)	185 (88.1%)	0.483
Pain (present)	7 (12.1%)	11 (5.2%)	0.078
LUTS (present)	18 (31.0%)	124 (59.0%)	< 0.001
Dysuria (present)	14 (24.1%)	131 (62.4%)	< 0.001
Bony pain (present)	1 (1.7%)	4 (1.9%)	1.000
SOB (present)	3 (5.2%)	2 (1.0%)	0.069
Jaundice (present)	0 (0.0%)	0 (0.0%)	1.000
LOW (present)	18 (31.0%)	86 (41.0%)	0.170
LOA (Present)	22 (37.9%)	80 (38.1%)	0.982
Tobacco use (present)	35 (60.3%)	158 (75.2%)	0.025
Alcoholism (present)	10 (17.2%)	106 (50.5%)	< 0.001
Occupational exposure to chemicals (present)	17 (29.3%)	92 (43.8%)	0.047
Family history of malignancy (present)	3 (5.2%)	8 (3.8%)	0.708
Chronic tea/coffee drinker (present)	5 (8.6%)	35 (16.7%)	0.128
Artificial sweeteners (present)	0 (0.0%)	5 (2.4%)	0.588
Chronic UTI (present)	3 (5.2%)	22 (10.5%)	0.219
DM (present)	0 (0.0%)	14 (6.7%)	0.045
HTN (present)	1 (1.7%)	107 (51.0%)	< 0.001
Other comorbidities			0.742
CAD	0 (0.0%)	4 (1.9%)	
CLD	0 (0.0%)	1 (0.5%)	
Parkinsonism	0 (0.0%)	1 (0.5%)	
Hemoglobin on presentation (g/dl)	11.20 ± 3.12	12.17 ± 2.45	0.056
Creatinine (mg/dl)	1.45 ± 2.42	0.96 ± 0.40	0.328

The most common risk factors associated with bladder cancer are smoking and tobacco consumption as well as occupational exposure to heavy metals. The associated rates of exposure in our study were 60.3% for smoking and 29.3% for occupational

exposure in the young population as compared to 75.2% and 43.8% respectively in the elderly population. Other risk factors like family history and chronic urinary tract infections were present in 5.2% of cases each in the young population as compared to 3.8% and 10.5%

Table 2 Imaging and cystoscopic characteristics and clinical staging of study participants

Parameters	Age group		p value
	≤ 40years (n = 58)	> 40years (n = 210)	
Number of lesions on imaging			0.629
1	46 (79.3%)	177 (84.3%)	
2	5 (8.6%)	12 (5.7%)	
≥ 3	7 (12.1%)	21 (10.0%)	
Tumour size on imaging (cm)	4.31 ± 2.31	2.78 ± 2.13	<0.001
Hydronephrosis (present)	20 (34.5%)	54 (25.7%)	0.186
T stage			0.957
<T2	38 (65.5%)	132 (62.9%)	
T2	3 (5.2%)	13 (6.2%)	
T3	5 (8.6%)	25 (11.9%)	
T4a	10 (17.2%)	34 (16.2%)	
T4b	2 (3.4%)	6 (2.9%)	
N stage			0.924
N0	45 (77.6%)	168 (80.0%)	
N1	1 (1.7%)	4 (1.9%)	
N2	6 (10.3%)	20 (9.5%)	
N3	6 (10.3%)	18 (8.6%)	
M stage			0.873
M0	51 (87.9%)	183 (87.1%)	
M1	7 (12.1%)	27 (12.9%)	
Size on cystoscopy (cm)			0.1741
<3	17 (29.3%)	82 (39.0%)	
>3	41 (70.7%)	128 (61.0%)	
Location			0.0402
Posterior wall	6 (10.3%)	31 (14.8%)	
Right posterolateral wall	30 (51.7%)	67 (31.9%)	
Left posterolateral wall	11 (19.0%)	73 (34.8%)	
Dome	1 (1.7%)	4 (1.9%)	
Trigone	0 (0.0%)	1 (0.5%)	
Anterior Wall	1 (1.7%)	13 (6.2%)	
Multiple Walls	9 (15.5%)	21 (10.0%)	
Morphology			0.2731
Solid	27 (46.6%)	81 (38.6%)	
Papillary	31 (53.4%)	129 (61.4%)	
Stalk			0.2671
Sessile	31 (53.4%)	95 (45.2%)	
Pedunculated	27 (46.6%)	115 (54.8%)	
Number			0.2261
Single	38 (65.5%)	119 (56.7%)	
Multiple	20 (34.5%)	91 (43.3%)	

respectively in the > 40 years group. Due to the chilly winters in northern India, there is a tendency of smoking from a younger age in this population as well as the exposure to smoke from firewood is also high which are most frequently used for cooking as well as to keep the indoors warm. This inhaled smoke could be a

postulated risk factor for the increased incidence of bladder cancer in this region [11]. Also, another possible exposure common to the people in this belt is the ground water consumption which most commonly comes from the mighty Ganges river known as the life-line of the northern plains of India [12]. Various geologic studies have reported a very high percentage of toxic heavy metals in the holy river namely lead, arsenic, nickel, chromium and iron, which are well known carcinogenic agents for bladder cancer. The effluents from various industries and factories find their way into the river and from there into the groundwater which is used for human consumption. The association of the drinking water being used in this north Indian belt and incidence of bladder cancer requires further studies to establish a causation. Thus the increased exposure to smoke through cigarettes, bidis, firewood etc. and exposure to chemicals and toxic heavy metals either through occupational exposure or through drinking water could explain the increased incidence of carcinoma bladder overall as well as in younger population of this gangetic belt of northern India.

A thorough literature search was done on studies that included young patients with bladder cancer. Twelve studies were identified in the last 20 years. Seven studies compared young and elderly population and five studies evaluated carcinoma bladder only in young patients (Table 4). Most of the studies reported in the literature thus far have reported than the carcinoma bladder in young adults is usually non muscle invasive and of low grade. Stanton et al. [13] reported that 83% of their patients younger than 30 years of age had non-muscle invasive bladder carcinoma (NMIBC). Woong et al. [14] showed a lower recurrence and progression rates for younger patients as compared to their elder counterparts, also they had a better prognosis as well as overall survival. Singh et al. [15] in their study revealed that 80% cases were NMIBC and 76% had a low-grade disease. In their study smoking, chronic tea/coffee consumption and exposure to dyes were significant risk factors. Yossepowich et al. [9] found that the stage distribution, grade distribution as well as progression rates were similar in the young population as compared to the older patients. Poletajew et al. [16], in their series on young adults with carcinoma bladder showed that 100% of their subjects had a NMIBC and Gunsuloy et al. [17] had 90% of young subjects with NMIBC. Sen et al. [18], Nomikos et al. [19] and Wang et al. [20] all highlighted the fact that the younger population of bladder cancer had a lower stage and a lower grade as compared to the older population. Telli et al. [21] emphasised on the fact that the 5-year overall survival for young population with bladder cancer reached almost 100%; however, an interesting point in their study was that although most of the cancers are low grade and stage, the ones which are more than 3 cm in size behave more aggressively than the smaller tumours.

A very recent retrospective study by De la Calle et al. [23] which identified over 3300 young patients from the National cancer database also concluded that most of the patients 18–40 years of age had a low-grade non-muscle invasive disease with better

Table 3 Histopathological characteristics and treatment of study participants

Parameters	Age group		<i>p</i> value
	≤ 40years (<i>n</i> = 58)	> 40years (<i>n</i> = 210)	
Tumour stage			< 0.001
T1	24 (41.4%)	121 (57.6%)	
Ta	13 (22.4%)	9 (4.3%)	
≥ T2	21 (36.2%)	80 (38.1%)	
Tumour grade			< 0.001
Low grade	21 (36.2%)	37 (17.6%)	
High grade	34 (58.6%)	173 (82.4%)	
PUNLMP	3 (5.2%)	0 (0.0%)	
CIS (present)	0 (0.0%)	0 (0.0%)	1.000
Deep muscle			0.793
Free	37 (63.8%)	130 (61.9%)	
Involved	21 (36.2%)	80 (38.1%)	
Histologic variant			0.909
Urothelial	51 (87.9%)	177 (84.3%)	
Urothelial with squamous differentiation	6 (10.3%)	26 (12.4%)	
Urothelial with sarcomatoid differentiation	1 (1.7%)	2 (1.0%)	
SCC	0 (0.0%)	2 (1.0%)	
Urothelial with glandular differentiation	0 (0.0%)	2 (1.0%)	
Urothelial with spindle cell component	0 (0.0%)	1 (0.5%)	
Staging and grading			< 0.001
PUNLMP	3 (5.2%)	0 (0.0%)	
T1 HG	13 (22.4%)	85 (40.5%)	
T1 LG	11 (19.0%)	36 (17.1%)	
T2 HG	21 (36.2%)	80 (38.1%)	
Ta HG	0 (0.0%)	8 (3.8%)	
Ta LG	10 (17.2%)	1 (0.5%)	
Type			0.793
MIBC	21 (36.2%)	80 (38.1%)	
NMIBC	37 (63.8%)	130 (61.9%)	
NMIBC risk			< 0.001
Low	11 (29.7%)	1 (0.8%)	
Intermediate	7 (18.9%)	0 (0.0%)	
High	19 (51.4%)	129 (99.2%)	
Treatment			< 0.001
BCG	24 (41.4%)	121 (57.6%)	
RC (with/without NACT)	6 (10.3%)	40 (19.0%)	
Palliative chemotherapy	6 (10.3%)	26 (12.4%)	
NACT	3 (5.2%)	11 (5.2%)	
Surveillance	11 (19.0%)	1 (0.5%)	
Expired (with/without treatment)	4 (6.9%)	7 (3.3%)	
Lost to follow-up	3 (5.2%)	4 (1.9%)	
Bladder preservation protocol	1 (1.7%)	0 (0.0%)	

survival. The results of our study have shown that bladder cancer in younger population less than 40 years of age is an aggressive tumour with almost 60% of the patients having a high-grade disease, 36.2% patients had a muscle invasive bladder cancer. Out of the 63.8% patients with a non-muscle invasive cancer, 51.4%

had a high risk on stratification. Also, 7 patients (12.1%) had a metastatic disease out of which 6 are receiving palliative chemotherapy and 1 expired. Thus, this study clearly highlights the aggressive and lethal behaviour of the disease even in younger population. As far as the elderly population was concerned, 60%

Table 4 Comparative review of literature showing staging and grading in various studies evaluating carcinoma bladder in young patients

S no	Study and year	Groups	n	Stage	Grade
1	Yossepowitch et al. [9]	<40 years	74	Ta–43.3% Tis–4.1% T1–35.1% T2–13.5% T3/4–4.1%	LG–48.7%, HG–51.3%
		>65 years	75	Ta–30.7% Tis–5.3% T1–38.7% T2–18.7% T3/4–6.6%	LG–30.7%, HG–69.3%
2	Nomikos et al. [19]	<40 years	31	Ta–74.2% T1–16.1% T2–6.4% T3–3.2%	LG–93.5% HG–6.4%
3	Poletajew et al. [16]	<41 years	27	Tis–0% Ta–100% T1–0% = /> T2–0%	G1–77.8% G2–22.1% G3–0%
		41–years	120	Tis–0.8% Ta–76.3% T1–11.9% = /> T2–11.0%	G1–30.5% G2–61.0% G3–8.5%
		>50 years	2013	Tis–2.4% Ta–62.7% T1–19.3% = /> T2–15.6%	G1–26.0% G2–56.8% G3–17.2%
4	Stanton et al. [13]	<30 years	59	PUNLMP–11.8% Ta LG–64.4% Ta HG–6.8% T1 HG–8.5% = /> T2 HG–8.5%	
5	Telli et al. [21]	<40 years	56	Ta–73.3% T1–19.6% T2–5.4% T3–1.7%	PUNLMP–28.6% LG–64.3% HG–7.1%
		>40 years	112	Ta–55.4% T1–19.6% T2–19.6% T3–5.4%	PUNLMP–16.9% LG–49.2% HG–33.9%
6	Woong et al. [14]	<40 years	42	Ta–78.6% T1–9.5% = /> T2–11.9%	LG–73.8% HG–26.2%
		>60 years	44	Ta–52.3% T1–36.4% = /> T2–11.4%	LG–47.7% HG–52.3%
7	Gunlusoy et al. [17]	<40 years	91	Ta–43.9% T1–47.2% T2–7.6% T3–1.2% T4–0%	G1–82.4% G2–4.3% G3–13.1%
8	Singh et al. [15]	20–40 years	31	Ta–48.3% T1–32.2% T2–19.3% T3–0% T4–0%	LG–80.7% HG–19.3%
		>60 years	79	Ta–7.5% T1–20.2% T2–36.7% T3–25.3% T4–10.1%	LG–53.1% HG–46.9%

Table 4 (continued)

S no	Study and year	Groups	n	Stage	Grade
9	Wang et al. [20]	< 30 years	42	Ta–90.5%, T1–9.5% T2–0% T3–0% T4–0%	LG–85.7%, HG–14.3%
		> 30 years	2783	Ta–66.8%, T1–13.3% T2–10.5% T3–6.2% T4–3.2%	LG–29.2% HG–70.8%
10	Sen et al. [18]	< 40 years	40	Ta–82.5% T1–15% T2–2.5%	LG–82.5% HG–17.5%
11	Perez et al. [22]	< 15 years	6	Ta 100%	Papilloma–16.6% PUNLMP–33.3% LG–50%
12	De la Calle [23]	18–40	3314	Tis–4.4% Ta–69% T1–16.9% T2–6.7% T3–1.2% T4–1.9%	LG–72.7%, HG–27.3%
		> 40	310,863	Tis–5.1% Ta–50.8% T1–25.4% T2–14.3% T3–2.0% T4–2.4%	LG–48.3%, HG–51.7%
13	Current study	< 40 years	58	Ta–22.4% T1–41.4% = / > T2–36.2%	PUNLMP–5.2% LG–36.2% HG–58.6%
		> 40 years	210	Ta–4.3% T1–57.6% = / > T2–38.1%	PUNLMP–0% LG–17.6% HG–82.4%

patients had NMIBC, and interestingly 99.2% of these cancers were stratified as high risk as per the guidelines. This finding further adds to the lethality and aggressive behaviour if the disease in this region. Out of the 14 patients < 40 years with non-metastatic MIBC, 6 were operable (defined as no T4b or N3 disease). Of these five did receive NACT and three of them underwent radical cystectomy and are doing well. Other two were lost to follow-up. Similarly in the elderly population, out of 53 patients with non-metastatic MIBC, 29 were fit to receive NACT. Of these, 17 underwent radical cystectomy with the remaining lost to follow-up due to various reasons.

Thus the results of the current study show that the young population also has an aggressive course of the disease with majority presenting with a high-grade and invasive disease contrary to previous studies. Environmental factors and exposure to carcinogens are significant factors responsible for this finding. The present study had its strength in the fact that it was a prospective study, however certain limitations need to be addressed. This is a single-centre, prospective study with a small sample size. Although the results may be applicable to one health system in India, these findings are

not generalisable to all countries and populations. Further prospective randomised studies are required to assess the clinical behaviour of bladder cancer in this cohort of patients.

In conclusion, it is noted that incidence of bladder cancer is on the rise in the northern belt of India along the gangetic plains, especially in the younger age group. High exposure to smoke via smoking/burning firewood and exposure to heavy metals through drinking water or occupation are the major risk factors. Majority of young patients aged < 40 years had a high-grade disease on presentation and a large subset had muscle invasive bladder cancer, contrary to previously reported studies. More randomised prospective studies are required to clearly elucidate the clinicopathologic biology in this age group for the early identification and management of the patients with worse prognosis.

Authors' Contributions The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Declarations

Conflicts of Interest The authors declare that there were no conflicts of interest.

References

- Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. *CA Cancer J Clin* 63:11–30
- Ploeg M, Aben KK, Kiemeny LA (2009) The present and future burden of urinary bladder cancer in the world. *World J Urol* 27:289–293
- American Cancer Society. *Global Cancer Facts. & Figures 4th Edition*. Atlanta: American Cancer Society; 2018.
- Stenzl A, Cowan NC, De Santis M, Kuczyk MA, merseburger AS, Ribal MJ et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. *Eur Urol* 2011;59:1009–18.
- Anastasiadis A, de Reijke T (2012) Best practice in the treatment of non-muscle invasive bladder cancer. *Ther Adv Urol* 4:13–32
- Vaidya A, Soloway MS, Hawke C et al (2001) De novo muscle invasive bladder cancer: is there a change in trend? *J Urol* 165:47–50
- Prout GR Jr, Griffin PP, Shipley WU. Bladder carcinoma as a systemic disease. *Cancer* 1979;43:2532–9.
- Wan J, Grossman HB (1989) Bladder carcinoma in patients age 40 years or younger. *Cancer* 6:178–181
- Yossepowitch O, Dalbagni G (2002) Transitional cell carcinoma of the bladder in young adults: Presentation, natural history and outcome. *J Urol* 168:61–66
- Ben-Abdallah M, Zehani S. 1994–2003 evolutions and projections by 2024. North Tunisia cancer registry: 1993–2003. *Tunisia*:25–31
- Pierson WE, Koenig JQ, Bardana EJ Jr (1989) Potential adverse health effects of wood smoke. *West J Med* 151(3):339–342
- Siddiqui E, Pandey J (2019) Assessment of heavy metal pollution in water and surface sediment and evaluation of ecological risks associated with sediment contamination in the Ganga River: a basin-scale study. *Environ Sci Pollut Res Int* 26(11):10926–10940
- Stanton ML, Xiao L, Czerniak BA, Guo CC (2013) Urothelial tumors of the urinary bladder in young patients: a clinicopathologic study of 59 cases. *Arch Pathol Lab Med* 137:1337–1341
- Na SW, Yu SH, Kim KH, Hwang EC, Jung SI, Kwon DD et al (2014) The prognosis of patients less than 40 years with bladder cancer. *J Can Res Ther* 10:710–714
- Singh JP, Priyadarshi V, Pal DK (2016) A clinicoepidemiological study of young age bladder tumors: an eastern Indian scenario. *J Can Res Ther* 12:751–754
- Poletajew S, Walędzia M, Fus L, Pomada P, Ciechańska J, Wasutyński A (2012) Urothelial bladder carcinoma in young patients is characterized by a relatively good prognosis. *Ups J Med Sci* 117:47–51
- Gunlusoy B, Ceylan Y, Degirmenci T, Kozacioglu Z, Yonguk T, Bozkurt H et al (2015) Urothelial bladder cancer in young adults: diagnosis, treatment and clinical behaviour. *Can Urol Assoc J* 9:E727–E730
- Sen V, Bozkurt O, Demir O, Esen AA, Mungan U, Aslan G, Kefi A, Celebi I. Clinical Behavior of Bladder Urothelial Carcinoma in Young Patients: A Single Center Experience. *Scientifica (Cairo)*. 2016;2016:6792484
- Nomikos M, Pappas A, Kopaka M-E, Tzoulakis S, Volonakis I, Stavrakakis G et al (2011) Urothelial carcinoma of the urinary bladder in young adults: presentation, clinical behavior and outcome. *Adv Urol* 2011:4
- Wang Z-H, Li Y-Y, Hu Z-Q, Zhu H, Zhuang QY, Qi Y et al (2012) Does urothelial cancer of bladder behave differently in young patients? *Chin Med J* 125:2643–2648
- Telli O, Sarici H, Ozgur BC, Doluoglu OG, Sunay MM, Bozkurt S et al (2014) Urothelial cancer of bladder in young versus older adults: clinical and pathological characteristics and outcomes. *Kaohsiung J Med Sci* 30:466–470
- Perez, Jaime & Chavarriaga, Julian & Peña, Paula & Ramos, Jose & Torres, Lynda & Bravo-Balado, Alejandra & Orrego, Paola & Fernandez, Nicolas. (2020). Transitional cell carcinoma of the bladder in pediatric patients: where do we stand?. *Urología Colombiana*. 29 <https://doi.org/10.1055/s-0039-3402486>
- de la Calle CM, Washington SL 3rd, Lonergan PE, Meng MV, Porten SP. Bladder cancer in patients younger than 40 years: outcomes from the National Cancer Database [published online ahead of print, 2020 Jul 31]. *World J Urol*. 2020; <https://doi.org/10.1007/s00345-020-03376-9>.

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