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Results: Multivariate logistic regression analysis revealed high tumor grade and multifocality as predominant predictors of tumor recurrence in young patients. A Significant difference was observed in the recurrence-free ($p < .018$) and progression- free ($p < 0.06$) survival rates between the two groups.

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Prognosis of Urinary Bladder TCC in Young Adults: A Single Center Experience

Urinary Bladder Cancer in Young Adults

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Conclusion: We concluded that although the clinical stage distribution, natural history, and outcomes of bladder TCC in young adults are similar to those in their older counterparts, Clinicians must be aware that patients with higher-grade and multifocal tumors are more likely to experience tumor recurrence and grade progression.

Keywords: TCC urinary bladder, recurrence, progression, grade, multifocality, smoking, recurrence- free survival, progression- free survival.

1. INTRODUCTION

Transitional cell carcinoma (TCC) urinary bladder is the fourth most common neoplasm in men and eighth most common neoplasm in women in the

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Western world. Urinary bladder cancer is rare in young Adults and occurs more commonly in elderly individuals. The median age of presentation for men is usually 69 yrs and for the female is 71 yrs respectively [1,2]. TCC urinary bladder incidence below the age of 40 years is 1% - 2.4% only. Younger population has incidence of only .1% - .4% (age less than 20 yrs) [3, 4]. Although the genomic nature and management of bladder cancer have been well researched, inconclusive reports exist about clinical pattern and prognosis for patients less than 40 years of age. Whether younger cases have a superior prognosis than their aged counterparts has long been a subject of contention; indeed, some reports projected similar patterns of clinical behavior and prognosis for TCC bladder in young and older patients, whereas other reports displayed lower rates of disease recurrence and progression, and superior outcome survival, in younger patients [5-8].

Among the probable risk scenarios expected in TCC bladder, tobacco consumption is most crucial and is responsible for 48% cases in males and 32% in females in the developed world [9]. Environmental factors in the form of occupational exposure, chemical and treatment exposure along with family history plays an important role in the etiopathogenesis of TCC bladder. In our analysis though majority of our patients were young tobacco consumers, we still noticed that a sizeable chunk did not have significant smoking exposure. The acute rise in these cases (NE India) in the past 2 decades bears testimony to the ever-increasing health hazards being faced by the population in this part of the world comprising of multiethnic population. An Indian study published data on patients diagnosed with TCC Urinary bladder and reported median age between 65–70 years. Moreover, there was a male preponderance (86.4% male vs. 13.6% female). Tobacco smoking (75% cases) revealed a strong relationship with TCC bladder which was quantity and duration dependent [9]. Another Indian study reported data collected from the Bombay Cancer Registry and found that bladder cancer was very uncommon in the first three decades of life [10]. Nonetheless, past 30 years of age, the incidence rates increase with age, in log-linear fashion, in both genders. The Indian

subcontinent data differ from the Western counterpart in two aspects. First, the contrast in the incidence of smoking among Indian men and women is much more distinguished (74% vs. 22%) than in the West. Second, the incidence of TCC bladder per se is much more cardinal in Indian men (8.9:1). The vast majority of bladder cancer in men versus women is explained by the smoking habits of men and estrogen-progesterone hormonal influence in the female reproductive life [11-14].

Most urinary bladder cancers consist of TCC, which can be classified into different categories with unique clinical pattern [15]. Low-grade, papillary lesions usually do not involve the muscle but often recur locally, demanding long-term surveillance. In contrast, high grade, non-papillary lesions are more prone for deeper invasion into the muscle layer and to metastasize, resulting in significant mortality. Contemporary studies have projected that papillary and non-papillary lesions may use various diabolical biological pathways, which may lead to their distinct biological manifestations [16]. Past analysis of patients with TCC bladder has used different denotation of young age, ranging from 20 years to 40 years. This diversion has led to inconsistent outcomes regarding the clinic-pathologic features of this dreaded disease in young individuals. Additionally, because TCC bladder is rare in young patients, most studies in these patients have been small series with the number of reported cases ranging from 12 to 50 [17]. To better characterize the clinic-pathologic features of TCC urinary bladder in young patients, we retrospectively evaluated a series of 71 cases in which clinical behavior, pathological outcomes, and disease recurrence and survival characteristics in patients with bladder TCC that were younger than 40 years of age. We compared our data with a matched cohort of young (Group A: ≤ 30 years Vs, Group B: 31- 40 years) patients with bladder TCC and intended to discover the difference in behavior of the disease between the two cohorts. The authors got on board to navigate the unexplored domain of TCC bladder with an aim to ascertain causality & risk factors predisposing to an early event, evaluate factors affecting disease recurrence and progression, estimation of survival characteristics and exact follow- up and radiological imaging schedule.

II. METHODS

After obtaining institutional ethics committee clearance, a retrospective review of our records between Jan 2006 and Dec 2012 identified 71 patients (43 males and 28 females) with transitional cell carcinoma of the bladder who were less than 40 years old. Clinical and pathological parameters of patients who were ≤ 30 years of age were compared with those of patients between 31- 40 years of age during the same period. Epidemiological and demographic data, including patient's age at presentation, gender, time of starting

and total duration of smoking, presenting clinical symptoms, initial HPE report, tumor size and locations, stages and grades at initial TURBT, recurrence events and disease progression to different grades or stages, and metastatic status, were collected. The 2004 WHO International Society of Urologic Pathology and 2002 tumor stage classification were used to evaluate the stages and grades of TCC bladder. Patients with nontransitional cell variety and upper tract TCC were excluded from the analysis. Disease recurrence was defined as the return of the disease at any site within bladder and progression was defined as upstage in tumor stage/grade. Moreover, recurrence or progression-free periods were defined as the dates of initial diagnosis of bladder cancer and those of disease recurrence or progression. Patients less than 40 years old were divided into two subgroups according to the age of presentation: younger than 30 years old and between 31 and 40 years old. Data among the groups were analyzed using the Chi-square test and Pearson's R test. Recurrence-free survival (RFS) & progression-free survival (PFS) analyses were performed using the Kaplan Meier method and log-rank test. Multivariate cox proportional hazards analysis, was outlined to identify independent predictors of the recurrence of TCC of the bladder in patients less than 40 years old. All statistical analyses were performed using SPSS version 21. A p value of <0.05 was considered statistically significant.

III. RESULTS

We analyzed all relevant data between Jan' 2006 and Dec' 2012 and 71 patients (43 men and 28 women) with TCC of the bladder who were ≤ 40 years old were included in the study with subgroup analysis of ≤ 30 years ($n=30$) and 31-40 years ($n=41$). For the two retrospective cohorts, the mean age at diagnosis was 24.21 years (range, 20.25- 28.57 years) and 37.66 years (range, 34.50-39.67) with an overall male to female ratio of 1.54:1. The mean \pm SD (overall) follow up time was 47.41 months (range, 12-65 months) (Table 2). Male and female distribution in the 2 groups is shown in Figure 1.

The mean (\pm SD) pack year for tobacco smoking in the age group ≤ 30 yrs was 30.22 ± 4.36 ($p=.418$) while that for age group ≤ 30 yrs was 10.25 ± 2.14 years. Similarly, mean \pm SD pack year for tobacco smoking in the age group 31-40 yrs was 44.63 ± 6.18 while mean \pm SD smoking duration for age group ≤ 30 yrs was 18.75 ± 5.14 yrs. The total number of active smokers in the group 1 was 53.3% while in the group 2 was 75.6% (Chi-square coefficient = 3.84, $p= .048$) (Table 1). Smoking was defined in the current study as > 100 cigarettes consumption overall as per the NIHS definition and was found to be significantly associated and correlated with TCC urinary bladder in the study (Pearson's $R = .233$, $p = .047$). Presence of risk factors was also ascertained and among all the risk factors

mentioned above, the presence of any one risk factor was considered positive, though not found to be significantly associated or correlated. There were 13.3% patients in the Group A (smoking + RF group), and 36.6% patients in the group B and both the groups were significantly associated and correlated with the same.

Macroscopic hematuria was the presenting symptom in 43.3% in the group A and in 58.5 % in the group B. Similarly, microscopic hematuria was the presenting symptom in 33.3% in the group A and 22 % in the group B. UTI / irritative voiding was the presenting symptom in 23.3% in the group A and 19.5 % in the group B (Figure 2). The mean time from the onset of symptoms to diagnosis was 38 days (range 14 – 67). Family history of TCC UB was present in 13.33 % (n=4) cases in group A and 10% cases (n=3) in the group B. History of neurogenic LUTD was present in 10 % (n=3) cases in group A and in 12.19% cases (n=5) in the group B. Mean tumor volume (USG) was $2.45 \pm .45 \text{ cm}^2$ (range: 2.20 – 3.2) for the entire study population. Majority of the patients (46.48%) had a tumor at the trigone (n= 33). Initial TURBT was done in all 71 cases. Re TURBT was done in 1 case (26.67%) in group A and in 5 cases (17.07%) in group B. TURBT + BCG was initiated in 8 cases (3.33%) in group A and in 7 cases (12.20%) in group B. Radical cystoprostatectomy (males) and anterior pelvic exenteration (female) with diversion followed by adjuvant chemotherapy was done in 8 case (19.51%) in group B. Radical TURBT + adjuvant chemo-radiotherapy in the form tri-modality therapy was initiated in 6.67% (n= 2) cases in group A and in 14.63 % (n= 6) cases in group B.

The clinical scenario of study population is presented in (Table 3). The most common T stage in the group A was Ta (70%) followed by T1 (23.3%) while in the group B, the incidence of both the groups was similar (23.3%). The distribution of the T stage in both the groups was not significantly associated or correlated (Table 2). Tumor grading (2004, ISUP) was distributed as low grade in 56.7% followed by high in 26.7% in the group A. In the group B however, the maximum number of cases were PUNLMP (43.9%) followed by a low grade as a distant second (31.7%). All these grade distributions were found to be significantly associated and correlated in the two groups (Table 4)]. Incidence of the high grade was almost similar in both the groups at 26.7% and 24.4% respectively, but it was found that the younger cohort had more high -grade and low-grade TCC's combined (Table 2) as compared to 31-40 years age group. Aforementioned result comes as a stark contrast to the belief that early age group behaves less aggressively then there aged counterparts as described in literature. Multifocal tumors were found to be present in 78% of the group B vis a vis 36.7% in the group A (significantly associated & correlated) (Table 4). Tumor size $\geq 2.5 \text{ cm}$ was seen in 20% cases in the group A and 14.6% cases in the group B. Tumor size

was not found to be significantly associated or correlated within the two respective groups (Table 4).

Tumor recurrence was seen in 16.7% cases in the group A and 43.9% in the group B and was significantly associated (Chi square coefficient =4.42, $p=.045$) and correlated (Pearson's R = .250, $p=.036$) (Table 5). One out of the total five recurrences (Ta, HG) in group A occurred within 3 months while the other 4 recurrence (Ta + T1, HG) occurred at 12 months. Nine out of the 18 recurrence in the group B (Ta + T1, HG) occurred within 3 months while 6/18 recurrence (Ta + T1, HG) occurred at 6 months. Three cases recurred between 18-24 months (Group B).

Tumor progression was seen in 6.7% cases in the group A and 36.6% in the group B and was significantly associated (Chi-square coefficient =7.12, $p=.011$) and correlated (Pearson's R =.346, $p=.003$). Among grade progression in the group A, one stage migration was observed from Ta to T1, and 1 from T1 to T2 and both occurred at 12 months of follow up. In the group B, 7 progressions from low grade to high grade TCC occurred at three months of follow up and five progressions from PUNLMP to Low grade at six months. Three cases progressed from low grade to high grade in between 18-24 months.

Multivariate logistic regression analysis projected tumor recurrence in study population with high-grade tumors [odds ratio (OR), 1.895; 95% confidence interval (CI),-.901-2.125; $p = 0.036$] and multifocality (OR, 2.310; 95% CI, .941-3.341; $p < 0.005$) (Table 6).The Kaplan Meier method was used to estimate the (RFS) recurrence free survival and (PFS) progression free survival. The 5-year RFS was 83% for group A and 56.1% for group B and the difference was found to be significant ($p= .018$) between the 2 groups. The 5-year PFS was 93.2 % for group A and 63.4 % for group B and the difference was found to be significant ($p= .005$) between the 2 groups.

IV. DISCUSSION

TCC urinary bladder in younger population (≤ 40 years) is a rare entity, with an incidence rate of only 0.8% [18]. There is a paucity of evidence regarding validated literature when comparing clinical pattern and outcomes of bladder TCC in younger patients especially ≤ 30 years and 31-40 years. To our knowledge there are hardly any studies except one or two regarding the subgroup analysis in population concerning TCC urinary bladder. As per the available studies the low- Ta tumor recurs at a rate of 50% to 70% and progress in 5% of cases while the high-grade T1 tumor recur in more than 80% of cases and progress in 50% of patients within 3 years. Our analysis in part confirm the reverberation of previous reports and projects that patients ≤ 30 years of age had less recurrence (20% as compared 44%, $p < .05$) and progression (6.7% as compared to 36.6%,

$p < .05$) than their counterparts in group B. This finding is supported by previous study results [19]. Notwithstanding the aforementioned fact, Group A did have high number of high grade TCC as compared to the group B. In our analysis, younger patients had more high-grade cancers than their aged counterparts (26.7% vs. 24.4%, $p < .05$) and more tumors >2.5 cm in size (20% vs. 14.6%), which was similar to the findings of previous retrospective studies [20]. Nonetheless, in the Surveillance, Epidemiology and End Results (SEER) database (1973 to 2003), of 140 bladder tumors affecting patients younger than 18 years old, 50.7% were diagnosed as PUNLMP. Thus, PUNLMP is regarded as the most common grade within this age group [21]. According to a recent analysis, although there is a preponderance of low-grade TCC in the first three decades of life, the grade distribution of TCC urinary bladder in older patients is not exactly comparable to those in the fourth decade of life which is also validated from our study results [22]. In our study, a male dominance was observed (male: female ratio 1.54:1) but which was below to those reported in previous analysis [23-25]. In both the groups under evaluation, the major presenting symptom was macroscopic hematuria with no significant difference between the younger and older patients. In a recent review of children with gross hematuria, causes of which consisted of infection, stones and malignancy, only three cases were diagnosed to have TCC bladder [26]. We have displayed in our analysis that stage distribution of patients aged 31-40 years with bladder TCC was not significantly different from their older counterparts, which is in concordance with some past published studies. In contrast, younger patients had slightly higher invasive disease which some studies indicated were due to CK20 along with mismatch repair proteins (MRPs) hMSH2, hMLH1, and hMSH6 along with FGFR3 [27]. We have analyzed our present data with the past studies and have found a comparable result thus validating our results (Table 7).

The Mantle Cox Log Rank was applied to estimate the five year RFS and five year PFS. The 5 yr RFS for the Group A was 83%, (Figure 3) while it was only 56.1 % for the Group B (Chi square 5.608, $p = .018$). The mean recurrence free survival was an estimated 55.84 months (95% C.I. – 49.32-62.36) for the group A while it was 43.40 months (95% C.I.: 35.91-50.89). The 5 yr PFS for the Group A was 93.2 %, (Figure 4) while it was 63.4 % grade.

For the Group B (Chi square 7.93, $p = .005$). The mean progression free survival was an estimated 61.84 months (95% C.I.: 57.90 - 66.02) for the group A while it was 48.74 months (95% C.I.: 42.18 - 55.30). To our misfortune, we could not do an extensive analysis because of the small number of cases, lack of sound

and apt information, and short follow-up period. Our study was limited by the fact that it was a retrospective study with inherent disadvantages, lack of CIS information in biopsy, lack of urine cytology information, correct age at start of smoking and exact duration of smoking before first symptom appearance and patient belonging to multiethnic groups.

V. CONCLUSION

TCC urinary bladder is a heterogeneous disease with high prevalence and recurrence rates. The present analysis provides useful reckoning of survival outcome, with aggressive treatments reserved for patients with higher stage disease. The analysis projected similar low grade TCC in both the groups but slightly higher high grade lesions in the younger Group A, though the exact reason is still under consideration. Multifocality and tumor grade were the predominant factors associated with early recurrence and progression. We found out that smoking alone and along with other risk factors (as confounding factor) contribute significantly to the recurrence and progression risk profile. We also concluded that a strict follow up at 3 month and till 12 months for low grade + PUNLMP is a bare minimum while it's strictly every 3 month for first 2 yrs for high grade lesion. Although this ontological event is less frequent in young adults, its effects remain substantial because these cases have a large chunk of their life still undiscovered and many responsibilities to fulfill. Since young age carcinoma exhibit a combination of features seen in younger and older patients, treatment protocol needs to evolve in such a way so as to provide prompt diagnosis and most suitable treatment scheme. Future endeavors focus on advancement of risk stratification and treatment protocols through clinical trials in young cases and implementation of effective prevention and early detection at middle ages.

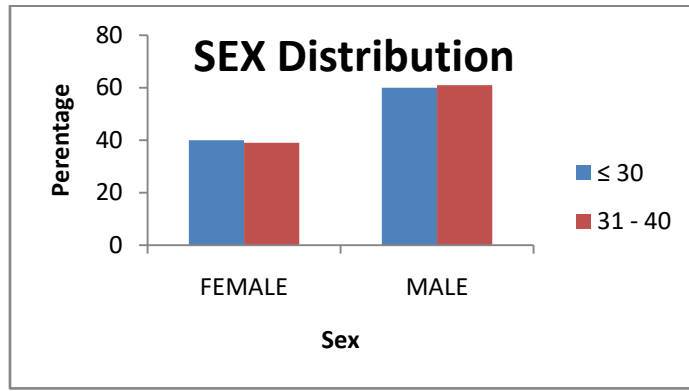


Figure 1: Showing gender distribution in the 2 subgroups

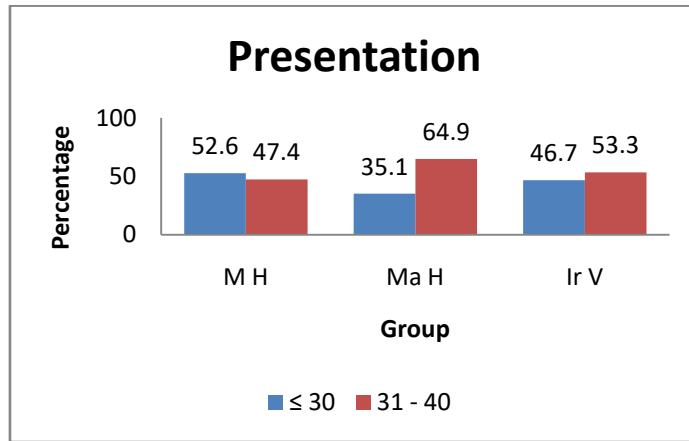


Figure 2 : Showing the clinical presentation in the 2 sub groups

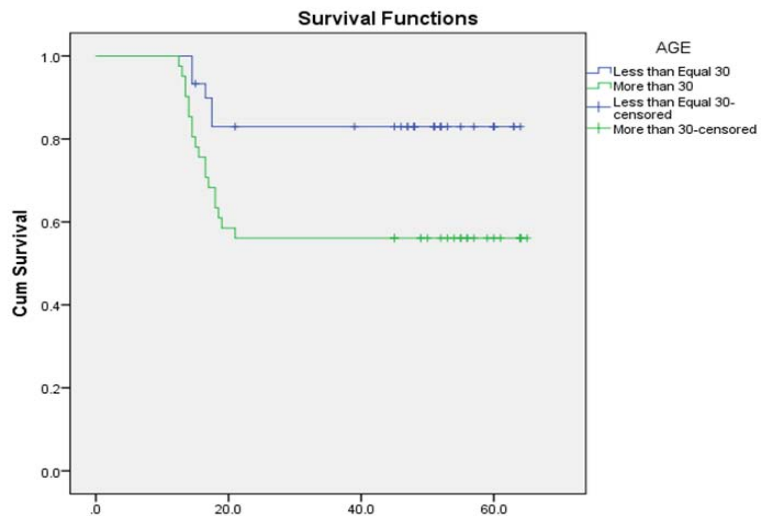


Figure 3: Showing the 5 Year RFS within Group A & B

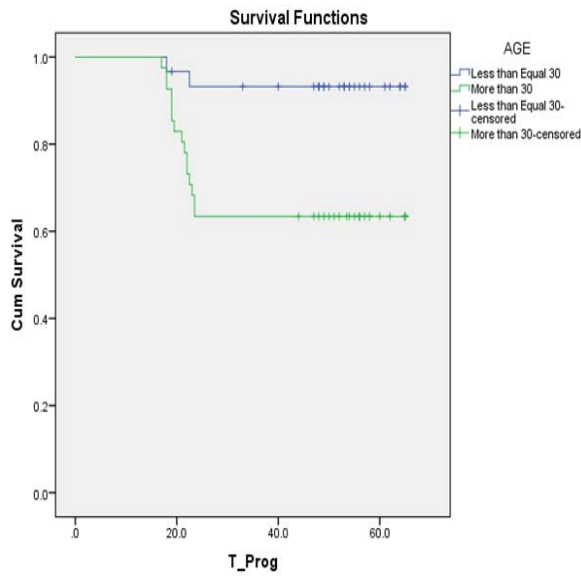


Figure 4: Showing the 5 Year PFS within Group A & B

Table 1: Showing the epidemiological and environmental pattern in both the subgroups

Variable	≤ 30 yrs n, (%)	31 – 40 yrs n, (%)	Total	Chi Square Coefficient	p Value
Patients	30 (42.3)	41 (57.7)	71		
Mean Age (range)			33.45(22 – 40)		
Sex (M/F)	18/12	25/16	43/28	.007	.934
Mean Follow Up (SD)	45.67± 11.40	49.15± 12.13	47.41 ± 12.74	.114	.430
Smoking (NHIS , > 100 cigarettes)	16 (53.3)	31 (75.6)	47 (66.2)	3.84	.048
Risk Factor*	10 (33.31)	19(46.3)	29(40.8)	1.213	.271
Smoking + Risk Factor	4 (13.3%)	15(36.6)	19(26.8)	4.77	.029

Table 2: Showing correlation of epidemiological data in the 2 groups.

Variable	Pearson R correlation Coefficient	p Value
Sex (M/F)	.010	.935
Mean Follow Up (SD)	.005	.847
Smoking (NHIS , > 100 cigarettes)	.233	.047
Risk Factor*	.131	.371
Smoking + Risk Factor	.259	.029

Table 3: Showing clinical parameters and distribution of T stage and grade in both the groups.

Variable	≤ 30 yrs n =30(42.3%)	31 – 40 yrs n =41(57.7%)	Total	Chi Square Coefficient	p Value
Clinical Presentation				1.72	.422
Microscopic Hematuria	10(33.3)	9(22)	19(26.8)		
Macroscopic Hematuria	13(43.3)	24(58.5)	37(52.1)		
Irritative voiding / UTI	7(23.3)	8(19.5)	15(21.1)		
T Stage				14.75	.060
Ta	21(70)	12(29.3)	33(46.5)		
T1	7(23.3)	12(29.3)	19(26.8)		
T2	2(6.7)	10(24.4)	12(16.9)		
T3	0	4 (9.8)	4 (5.6)		
Grade				16.56	.039
PUNLMP	5(16.7)	18(43.9)	23(32.4)		
Low Grade	17(56.7)	13 (31.7)	30 (42.3)		
High Grade	8(26.7)	10(24.4)	18(25.4)		
Multifocal				12.42	.001
>1 lesion	11(36.7)	32(78)	43(60.6)		
Tumor Size (≥ 2.5 cm)	6(20)	6(14.6)	12(16.9)	.355	.550

Table 4: Showing clinical parameters and correlation in both the groups.

Variable	Pearson R correlation Coefficient	p Value
Clinical Presentation		
Microscopic Hematuria	.054	.654
Macroscopic Hematuria		
Irritative voiding / UTI		
T Stage	.873	.114
Grade	4.52	.001
Multifocal >1 lesion	.488	.001
Tumor Size (≥ 2.5 cm)	.071	.350

Table 5: Showing tumor recurrence and progression in both the subgroups

Variable	≤ 30 yrs n =30(42.3%)	31 – 40 yrs n =41(57.7%)	Total	Chi Square Coefficient	p Value
Tumor recurrence	5(16.7)	18 (43.9)	24 (33.8)	4.42	.045
Tumor Progression	2(6.7)	15 (36.6)	17(23.94)	7.12	.011

Table 6: Multivariate cox regression analysis depicting significant variable predicting recurrence in young population

Variable	Odds ratio	95% C.I.	p Value
Sex (Male) (Female)	.984 1.025	.672 – 1.441 .573 – 1.815	.071
Grade PUNLMP Low Grade High Grade	1.000 1.013 1.895	.901 – 2.125	.036
T Stage Ta/T1 T2/T3	1.011 1.781	.810 – 1.954	.065
Multifocality ≤ 1 lesion >1 lesion	1.000 2.310	.941-3.341	.005
Tumor Size ≤2.5 cm >2.5 cm	.918 1.101	.814- 1.245	.544

Table 7: Comparison of vital statistics of the present study with past retrospective analysis

Author	Number of cases	Mean follow up (months)	Superficial Bladder Cancer (%)	Invasive Bladder Cancer (%)	Recurrence (%)	Progression (%)
Wen et al. ¹²	30	72.8	76	23.4	50	8.3
Yossepowitch et al. ¹⁴	74	28.1	83	16.6	38.7	16
Erozenci et al. ²⁸	156	87	89.1	10.9	48.7	22.8
Perez et al. ²⁹	30	66	67.6	23.3	32	0.1
Present Study	71	45	73.2	33.8	33.8	23.94

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Conflict of interest: None

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