ORIGINAL ARTICLE



# **Clinicopathologic Comparison of Urothelial Bladder Carcinoma** in Young and Elder Patients

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Abstract Bladder cancer (BC) is a common aggressive malignancy and Urothelial bladder cancer (UBC) consists of the majority of BC. There is uncertainty regarding the clinicopathologic characteristics of UBCs in younger patients. To investigate the clinicopathologic features of young patients with UBCs. A total of 2825 pathological records of UBC patients, including 42 young patients ( $\leq$  30 years old) and 2783 elder patients (> 30 years old), were retrospectively studied. The stage distribution classified was statistically significant ( $X^2 = 12.25, P = 0.02$ ) between young and old patients; superficial tumors was far more in young patients than in old patients. More young patients tended to be low- and moderate-grade UBCs ( $X^2 = 6.75$ , P = 0.009). Young patients with superficial UBCs also showed lower recurrence rate, compared to elder patients ( $X^2 = 5.77, P = 0.02$ ). For 5-year survival rate, young patients (93.8 %) showed better than elder patients (85.1 %) ( $X^2 = 4.01$ , P = 0.045). Patients younger than 30 years old with UBCs had low-grade and low-stage tumors and exhibited better prognosis than elder patients.

Keywords Urothelial bladder cancer · Young · Pathology

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#### Introduction

Bladder cancer (BC) is a common malignancy and its incidence has been steadily increasing with an estimated 74,690 new cases and 15,580 deaths in 2013 globally [1],. Though smoking [2], exposure to aromatic amine and polycyclic aromatic hydrocarbons [3], and genetic variations [4, 5] were widely agreed to increase the risk of BC, its etiology and carcinogenesis remains unclear.

Urothelial bladder cancer (UBC) consists of the majority of BC. Overall, 70 % of UBC present as low-grade and superficial tumors, while the remaining carcinomas are high-grade and muscle-invasive tumors [6]. UBCs is typically a disease of older individuals, with the median age of the first diagnosis 69 and 71 years old for males and females respectively, and rarely occurs below the age of 40 years [7]. There is debate and uncertainty regarding the clinicopathologic characteristics of UBCs in younger patients [8–13]. Some studies reported a more favorable prognosis in young patients compared to old patients [14]; while other studies showed similar clinical course of UBCs in young and old patient groups [9, 11]. One reason for the inconsistence would be different definitions of young age, which ranged from 20 to 40 years in the previous studies [10, 13, 15].

In the present study, we retrospectively evaluated a large series of patients initially diagnosed at age of 15–99 years old to compare the features of UBCs in young patients and old patients.

## **Materials and Methods**

### Subjects

A total of 2825 pathological records of UBC patients in our institution in the period January 1983 to May 2014 were

retrospectively analyzed. For each patient, the tumor grade was determined using the 2004 World Health Organization classification system and the stage was determined based on the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification, 7th edition [16]. Detailed data, including histologic features, demographic information, medical history, tumor recurrence, clinical outcome and so on, was collected.

This study was approved by the Institutional Review Board of our institution (project No. S-236).

## Statistics

The programs Graphpad Prism 5, SPSS 17.0, and Microsoft Office Excel 2007, were used for data analysis. The data are presented as mean  $\pm$  SD for continuous variables or percentages for categorical variables. The Chi-squared test was used to analyze correlations of all variables. A *P*-value of less than 0.05 was considered statistically significant.

#### Results

#### **Demographic Information**

For all patients, the mean age was 64.11 years old (Fig. 1). For further analysis, patients were divided into two groups depending on age of diagonosis: group 1 (age  $\leq 30$ , N = 42) and group 2 (age > 30, N = 2783) (Table 1). The mean age of group 1 and group 2 was 24.8 years and 64.7 years, respectively. Twenty-seven patients, constituting 64.3 % of all patients, were male in group 1; while in group 2, male patients constituted 75.1 % of all patients. Though incidence of women UBCs slightly increased in group 2, there was no significant difference in sex distribution between group 1 and group 2 (P = 0.11). 73.8 % of patients in group 1 (31/42) and 78.6 % of patients in group 2 (2187/2783) complained of intermittent gross hematuria as their leading symptoms, the percentage are comparable in both groups. As for recurrent treatment for the followup patients, TURBt was used in 93.8 % (30/32) of



Fig. 1 Patient age distribution

 Table 1
 Age and sex distribution in the study group

	Group 1	Group 2	P-value
Number of patients	42	2783	
Age of onset (Mean $\pm$ SD)	$24.8\pm4.2$	$64.7\pm12.1$	
Males (N, %)	27 (64.3 %)	2089 (75.1 %)	0.11

patients in group 1 and in 89.7 % of patients in group 2 (2020/2253) and there is no statistic difference between them. However, the percentage of patients who have years of smoking history is very significantly higher in group 2 than that in group 1 (66.8 %, 1859/2253 vs. 26.2 %, 11/42, p < 0.01).

## **Tumor Stage and Grade**

According to the TNM staging system, we divided the patients of group 1 and 2 into 5 subgroups, namely Ta, T1, T2, T3 and T4 subgroup. The number of patients falling into each subgroup was described in Table 2. In group 1, 42 patients (100 %) had superficial tumors (Ta and T1); while in group 2, 80.1 % of patients had superficial tumors and 19.9 % of patients had muscle invasive tumors (T2 – T4). The stage distribution classified by TNM system was statistically significant ( $X^2 = 12.25$ , P = 0.02). Interestingly, we observed no muscleinvasive cancer amongst the young patients.

Moreover, when we divided the patients of each group into two grades, namely low-grade and high-grade, the number of each grade showed substantially different between two groups  $(X^2 = 6.75, P = 0.009)$  (Table 2). In group 1, low-grade tumors accounted for 85.7 %; while in group 2, high-grade tumors reach up to 70.8 %.

## **Outcome of Patients with UBCs**

Cystectomy or cysto-prostatectomy was performed in 35 patients and 2474 patients among group 1 and group 2,

 Table 2
 TNM stages and grades

Parameter/subgroup	Group 1 $(age \le 30)$	Group 2 (age > 30)	$X^2$	Global P-value
T stage			12.25	0.02
Ta (N, %)	38 (90.5)	1859 (66.8)		
T1 (N, %)	4 (9.5)	371 (13.3)		
T2 (N, %)	0 (0)	291 (10.5)		
T3 (N, %)	0 (0)	173 (6.2)		
T4 (N, %)	0 (0)	89 (3.2)		
Tumor grade			6.75	0.009
Low-grade	36 (85.7)	813 (29.2)		
High-grade	6 (14.3)	1970 (70.8)		

respectively. Follow-up information was obtained for 2285 individuals, with 32 patients in group 1 (32 superficial and 0 invasive) and 2253 patients in group 2 (2028 superficial and 225 invasive). The mean follow-up time was 52 months, ranging from 3 to 120 months.

The recurrence rates for superficial UBCs in the two groups were 34.3 % (group 1) and 51.1 % (group 2) (Table 3). Thus, statistically significant difference was identified between the two groups, and disease recurrence, especially of superficial bladder cancer, increased greatly in older than younger patients ( $X^2 = 5.77$ , P = 0.02). Besides, the recurrence rate of invasive UBCs in group 2 was 70.2 %, more than superficial UBCs.

The proportion of 5-year survival rate was 93.8 % for younger patients and 85.1 % for older patients (Table 3). Chi-square test showed significant difference between the two groups ( $\chi^2 = 4.01$ , P = 0.045).

## Discussion

In this study, we retrospectively analyzed and compared UBC features in a large number of young patients vs. old patients. Our study is special since o the best of our knowledge, the sample size of our study is the largest to date, which conferred more convince to our result.

Slawomir et al. found that the incidence of UBC in women increased with age [17]. For detail, male-to-female ratio was calculated to be 4.4 in younger group (age  $\leq$  40), while this ratio decreased to 2.9 in older group (age  $\geq$  60). Aboutaieb et al. also reported similar results [18]. Interestingly, the opposite result was also reported. Migaldi et al. have reported that women constituted 32 % of patients with age less than 45 years and 12 % amongst elderly patients aged  $\geq$  45 [8].However, in our study, We have not found any difference in gender distribution between younger and elder groups which is not in line with studies mentioned above. We have to point out that due to the fact that younger patients only account for a small part in all the studies, including our study, thus, it is difficult to conclude whether gender distribution in the two groups is different or not.

In our study, that the proportion of low-grade UBCs was higher in young patients than that in old patients and this is consistent with many other studies [12, 19]. Chang et al.

Table 3 Outcomes of UBC patients

	Group 1	Group 2	$X^2$	P-value
Total of follow-up patients	32	2253		
Recurrence rate				
Superficial (N, %)	12 (34.3)	1037 (51.1)	5.77	0.02
Invasive (N, %)	0 (0)	158 (7.0)		
5-year survival rate	30 (93.8)	1917 (85.1)	4.01	0.045

revealed that six out of eight UBC patients aged < 40 years had low-grade tumors [12]. Lerena et al. also reported a 100 % incidence of low-grade UBCs in children [19]. Moreover, we further found the difference in stage of UBCs according to age. All patients in young group were superficial tumors, while only 80.1 % old patients had superficial tumors and the remaining had invasive UBCs. This finding is also consistent with studies by others [11, 20].

Of particular interest, we found that UBC recurrence was age-related and tended to occur more frequently in older than younger patients. Also smoking habit correlated with the poor prognosis of patients with UBC in elder patient group. For superficial UBCs, recurrence of group 1 was 34.3 %, which was lower than that in group 2 (51.1 %). Other results are further supported by other study. Wen et al. also reported that the recurrence rates for UBC higher in elder patients (elder 52.7 % vs. younger 40 %0 [21].

Despite this is the largest series of patients with UBC, We would like to emphasize that the number of young patients was still relatively small. Further studies are needed to confirm our results.

In short, patients younger than 30 years old with UBCs usually have low-grade and low-stage tumors. Their recurrence rate was also lower than older patients. This study highlights the importance of age and smoking habits on survival of patients with UBC and might be helpful for urologists to manage young patients with UBC.

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**Conflict of Interest** The authors declare that they have no conflict of interest relating to the publication of this manuscript.

#### References

- Siegel R et al. (2014) Cancer statistics, 2014. CA Cancer J Clin 64(1):9–29
- Shakhssalim N et al. (2010) Prominent bladder cancer risk factors in Iran. Asian Pac J Cancer Prev 11(3):601–606
- Olfert SM, Felknor SA, Delclos GL (2006) An updated review of the literature: risk factors for bladder cancer with focus on occupational exposures. South Med J 99(11):1256–1263
- Tajuddin SM et al. (2014) LINE-1 methylation in leukocyte DNA, interaction with phosphatidylethanolamine N-methyltransferase variants and bladder cancer risk. Br J Cancer 110(8):2123–2130
- Liu C et al. (2013) XRCC1 Arg194Trp and Arg280His polymorphisms in bladder cancer susceptibility: a meta-analysis. Crit Rev Eukaryot Gene Expr 23(4):339–354
- Kirkali Z et al. (2005) Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 66(6 Suppl 1):4–34
- Jemal A et al. (2010) Cancer statistics, 2010. CA Cancer J Clin 60(5):277–300
- Migaldi M et al. (2004) Superficial papillary urothelial carcinomas in young and elderly patients: a comparative study. BJU Int 94(3): 311–316

- Kutarski PW, Padwell A (1993) Transitional cell carcinoma of the bladder in young adults. Br J Urol 72(5 Pt 2):749–755
- Fitzpatrick JM, Reda M (1986) Bladder carcinoma in patients 40 years old or less. J Urol 135(1):53–54
- Yossepowitch O, Dalbagni G (2002) Transitional cell carcinoma of the bladder in young adults: presentation, natural history and outcome. J Urol 168(1):61–66
- Chang SY, Ma CP (1987) Transitional cell carcinoma of the urinary bladder in patients under 40 years of age. Br J Urol 60(4):343–344
- Fine SW et al. (2005) Urothelial neoplasms in patients 20 years or younger: a clinicopathological analysis using the world health organization 2004 bladder consensus classification. J Urol 174(5):1976–1980
- Keetch DW, Manley CB, Catalona WJ (1993) Transitional cell carcinoma of bladder in children and adolescents. Urology 42(4):447–449
- Stanton ML et al. (2013) Urothelial tumors of the urinary bladder in young patients: a clinicopathologic study of 59 cases. Arch Pathol Lab Med 137(10):1337–1341

- Edge SB, Compton CC (2010) The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17(6):1471–1474
- Poletajew S et al. (2012) Urothelial bladder carcinoma in young patients is characterized by a relatively good prognosis. Ups J Med Sci 117(1):47–51
- Aboutaieb R et al. (1998) Bladder tumors in young patients. Prog Urol 8(1):43–46
- Lerena J et al. (2010) Transitional cell carcinoma of the bladder in children and adolescents: six-case series and review of the literature. J Pediatr Urol 6(5):481–485
- Iori F et al. (2001) Superficial bladder tumors in patients under 40 years of age: clinical, prognostic and cytogenetic aspects. Urol Int 67(3):224–227
- Wen YC et al. (2005) Urothelial carcinoma of the urinary bladder in young adults-clinical experience at Taipei veterans general hospital. J Chin Med Assoc 68(6):272–275