

# Predictive Factors for Prostatic Involvement by Transitional Cell Carcinoma of the Bladder

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**Purpose:** To evaluate the predictive factors for prostatic involvement according to the bladder transitional cell carcinoma (TCC) characteristics in a prospective study.

**Materials and Methods:** Hundred patients with the bladder TCC who had undergone standard radical cystoprostatectomy were enrolled in this study. A number of factors, including vascular and perineural invasion, number of tumors, maximum diameter of the tumor, presence of carcinoma in situ, distance between the tumor and the bladder neck, grade, and local stage of the tumor were recorded, and their relationships with prostatic involvement were studied. In addition, hydronephrosis and age of the patients were included in the analysis.

**Results:** The mean age of the patients was  $62.6 \pm 10.8$  years. Of a total of 100 patients, 21 (75%) were found to have prostatic involvement with TCC. Univariate statistical analysis showed that vascular invasion and the distance between the tumor and the bladder neck were significantly related to the prostatic involvement ( $P = .001$  and  $P < .001$ ) and tumor stage had relatively low  $P$  value ( $P = .08$ ). In the logistic regression, only the distance between the tumor and the bladder neck was found to be significantly related to the prostatic involvement ( $P = .004$ ).

**Conclusion:** This study demonstrated that distance between the tumor and the bladder neck is a predictive factor for prostatic involvement; hence, prostate-sparing or capsule-sparing cystectomy in patients with tumors in short distances from prostatovesical junction is not rationale and should be avoided.

Keywords: urinary bladder neoplasms, transitional cell carcinoma, cystectomy, prostate

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## INTRODUCTION

Primary transitional cell carcinoma (TCC) in the prostate is rather uncommon (3%) and the prostate is usually involved by expansion of the bladder cancer.<sup>(1)</sup> Previously, prostatic involvement through bladder TCC has been reported in 7% to 48% of the patients undergoing radical cystectomy.<sup>(1-3)</sup>

A number of studies have evaluated long-term survival,

organ preservation protocol, and functional outcomes of surgery in invasive bladder cancer. They concluded that radical cystoprostatectomy is an ideal alternative to treatment of muscle-invasive bladder cancer.<sup>(4,5)</sup> Sexual dysfunction, including erection, ejaculation, and fertility issues, due to cutting of neurovascular bundle during excision of the prostate and incontinency are the most

important concerns in this procedure; hence, modified techniques have gained broad attention.<sup>(5)</sup>

The use of nerve-sparing radical cystectomy in selected patients has led to proper clinical and functional outcomes without compromising cancer control.<sup>(6)</sup> Preservation of sexual function and continence improvement, especially for nighttime,<sup>(7)</sup> have encouraged urologists to perform prostate-sparing radical cystectomy with neobladder reconstruction.<sup>(8)</sup> Using prostate-sparing technique without suitable case selection through determining prognostic factors before operation leads to risky events, such as higher local and distant recurrences.<sup>(9)</sup>

In this prospective study, we decided to complete our previous survey performed in 2005<sup>(10)</sup> by using a larger group of patients and evaluating the relationship between different variables of the bladder TCC and the risk of the prostatic involvement.

## MATERIALS AND METHODS

Between January 2003 and February 2007, this prospective study was performed in Shahid Labbafinejad Medical Center. All patients with proven bladder TCC who underwent standard radical cystoprostatectomy with en bloc excision of the bladder, the prostate, and the seminal vesicles were included in this study. Patients with a history of previous surgery on the bladder or the prostate, systemic chemotherapy, and previous pelvic or lower abdominal radiotherapy were excluded. One hundred patients, who had the inclusion criteria, were enrolled in the study and written informed consents were taken from each of them.

Pathologic examination was performed by a single pathologist. Characteristics of the tumors, including the number of the tumors (single or multiple), maximum diameter of the tumors in centimeter, tumor distance from the bladder neck (TD), existence of carcinoma in situ (CIS), tumor grade (low or high), local stage (non muscle invasive, T2, T3, and T4), and vascular and perineural invasion were also recorded. Prostatic involvement by TCC was also assessed by the same pathologist.

Presence of hydronephrosis was assessed by

pre-operative ultrasonography or computed tomography scan. Prostatic involvement was classified into three subgroups, including urethral invasion, stromal invasion, or both.

Statistical analysis was performed by SPSS (Statistical Package for the Social Sciences, Version 13, SPSS Inc., Chicago, Illinois, USA) software. Relationship between each single factor and the prostatic involvement was evaluated by Chi-square test. The differences in age and TD between the patients with or without prostatic involvement were analyzed by the student's *t* test and Kolmogorov-Smirnov test. All factors that assumed to have significant effects were analyzed by using logistic regression (backward Wald method) afterwards. The receiver operating characteristic curve was used to select a cutoff point with the best diagnostic accuracy for continuous variables.

## RESULTS

The mean age of the patients was  $62.6 \pm 10.8$  years at the time of surgical operation. Of a total of 100 patients, 28 had prostatic involvement: 21 (75%) subjects had TCC in their prostates and 7 (25%) had adenocarcinoma. Of 21 patients with prostatic TCC, 8 (38.2%) had TCC in the urethra, 6 (28.5%) in the stroma, and 7 (33.3%) in both.

The characteristics of the patients and the tumors in the two groups of positive and negative prostatic involvement are shown in Table. Univariate analysis demonstrated that from the assessed ten factors, only vascular invasion ( $P = .001$ ; odds ratio, 5.13; 95% confidence interval, 1.85 to 14.24) and TD ( $P < .001$ ; odds ratio, 7.74; 95% confidence interval, 2.37 to 25.26) had significant relationships with the prostatic involvement. In the second step, vascular invasion and TD in addition to the tumor stage were entered into the logistic regression model. We calculated tumor stage in association with two aforesaid factors because of its relatively small *P* value ( $P = .08$ ) and the fact that it had been found to be a significant factor in some previous studies.<sup>(11)</sup> The logistic regression analysis showed that only TD had a significant relationship with the prostatic involvement ( $P = .004$ ). The receiver operating characteristic curve showed

Characteristics of patients with bladder TCC<sup>†</sup>

Factors	Prostatic Involvement <sup>†</sup>		P	Odds Ratio	95% Confidence Interval
	Positive	Negative			
Age, mean, y	62.8 ± 11.45	62.5 ± 10.7	.92	...	-5.96 to 5.42
TD, mean, cm	0.40 ± 0.38	1.34 ± 1.13	< .001	7.74	2.37 to 25.26
Tumor stage					
Non muscle invasive	3 (14.3)	22 (27.8)			
T2	9 (42.9)	35 (44.3)			
T3	5 (23.8)	19 (24.1)			
T4	4 (19.0)	3 (3.8)	.08	...	...
CIS	7 (33.3)	24 (30.4)	.79	1.14	0.41 to 3.20
Vascular Invasion	13 (61.9)	19 (24.1)	.001	5.13	1.85 to 14.24
Perineural Invasion	7 (33.3)	22 (27.8)	.62	1.29	0.46 to 3.63
Multifocal disease	12 (57.1)	31 (39.2)	.14	3.14	0.78 to 5.47
High grade disease	15 (71.4)	47 (59.5)	.32	1.07	0.60 to 4.85
Hydronephrosis	8 (38.1)	27 (34.2)	.74	1.18	0.44 to 3.21
Tumor diameter ≥ 2 cm	17 (81.0)	66 (83.5)	.50	0.84	0.24 to 2.90

\*TCC indicates transitional cell carcinoma; TD, tumor distance from the bladder neck; and CIS, carcinoma in situ.

<sup>†</sup>Values in parentheses are percents.

high sensitivity and specificity (area under the curve: 0.78 – sensitivity: 81.0%, specificity: 74.6%) (Figure), and the odds ratio for a TD less than 0.65 cm was 7.74.

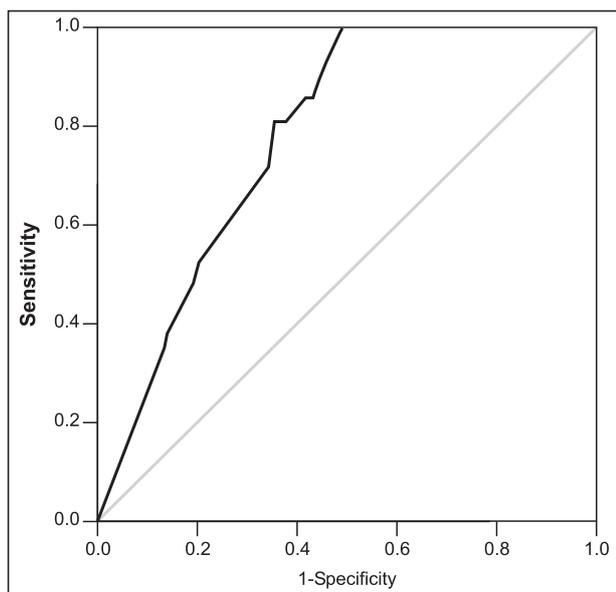
## DISCUSSION

Invasive bladder TCC as a life-threatening disease is associated with high mortality rate if left untreated. Aggressive surgical treatment by performing radical cystectomy, in comparison with the organ preservation modality and

chemoradiotherapy, has better long-term survival and lower local recurrences.<sup>(12,13)</sup>

Previously, patients who underwent radical cystoprostatectomy would suffer from comprehensive morbidity, such as incontinency, sexual dysfunction, and infertility problems, especially if they were young; thus, a large number of patients refused to accept this treatment. After considerable advance in surgical techniques and using orthotopic urinary diversion with acceptable functional outcomes and significant impact on the quality of life in the majority of patients,<sup>(14)</sup> the patients were encouraged to undertake radical cystectomy. Nerve-sparing radical cystoprostatectomy has been performed with good results and improved sexual function without compromising the cancer control.<sup>(6)</sup> Prostate-sparing cystectomy has been advocated rationally because of preserving the potency, fertility, and continency.

Average incidence of prostatic involvement by TCC by routine selective sections was 21.8% (nearly similar to our result: 21%) and 36.7% by whole mount sections.<sup>(15)</sup> Pagano and colleagues defined two distinct clinicopathological features for prostatic involvement by bladder TCC: stromal invasion either by extravescical extension of the bladder tumor (PT4a) or secondary to prostatic urethral involvement.<sup>(16)</sup> Schellhammer and associates revealed that long-term survival significantly would depend on the presence



Receiver operating characteristic curve shows the sensitivity and 1 - specificity of the tumor distance from the bladder neck for the prostatic involvement by transitional cell carcinoma.

or absence of stromal invasion (22% versus 50%).<sup>(17)</sup> Njinou Nginkeu and coworkers in a retrospective study on 76 patients demonstrated that invasion by direct extension from the prostatic urethra has better prognosis than extension from the bladder wall (49% versus 29% free survival rate).<sup>(18)</sup> But Ayyathurai and colleagues emphasized that depth of invasion (stromal versus non-stromal) is more important than mode of invasion.<sup>(19)</sup>

Spitz and associates performed the prostate-sparing approach on 4 patients for the first time.<sup>(20)</sup> Vallancien and coworkers treated 100 patients with the bladder TCC by this technique; however, they did not delineate predictive factors. Therefore, indications for excluding the patients were based on abnormal prostate biopsy according to abnormal digital rectal examination or serum prostate-specific antigen.<sup>(21)</sup>

Hautmann and Stein matched the pathological stage of 252 patients who underwent prostate-sparing procedure with the other 646 patients who had standard radical cystectomy. They inferred that distant recurrence in the first group was twice the second one.<sup>(9)</sup> In another study, 25 patients who underwent the prostate-sparing cystectomy with normal serum level of prostate-specific antigen and negative transurethral resection of the prostate had worse cancer control and better functional outcomes than standard radical cystectomy.<sup>(22)</sup>

There are different comments on the role of pre-operative transurethral biopsy of the prostate to detect the prostate invasion by the bladder TCC;<sup>(15,23)</sup> thus, attentions have been attracted to the clinicopathological characteristics of the bladder TCC for predicting the prostatic involvement. Nixon and colleagues argued that of 159 patients evaluated by pre-operative cystoscopy, only 5 subjects who were believed to have normal urethra had prostatic carcinoma.<sup>(24)</sup> Several studies concentrated on clinicopathological characteristics of the bladder TCC to predict the prostatic involvement for determining the type of urinary diversion and/or the prostate-sparing. Basiri and coworkers reported that grading and staging of the primary tumor have considerable correlation with the prostate invasion.<sup>(25)</sup> In other

study, presence of CIS and tumor multifocality had prognostic values for prostatic urethral involvement.<sup>(24)</sup> Recently, Patel and associates reported that 39.3% of patients undergoing radical cystectomy had different types of urothelial prostatic involvement. Furthermore, CIS and trigonal invasion of the bladder tumor were major risk factors for the prostatic involvement.<sup>(26)</sup>

In our study, univariate analysis demonstrated that of the assessed factors, only vascular invasion ( $P = .001$ ) and TD ( $P < .001$ ) had significant correlation with the prostatic involvement and the logistic regression analysis showed that only TD had a significant effect on involvement of the prostate by TCC ( $P = .004$ ). These results are nearly similar to our previous analysis on 60 patients, but the important difference is the cutoff point of 0.65 cm for TD in comparison to 0.55 cm in the previous assessment.<sup>(10)</sup>

This prospective study showed that distance between the tumor and the bladder neck in pre-operative cystoscopy has considerable value for managing the bladder TCC, determining the type of urinary diversion, and the use of prostate-sparing technique. Due to the possibility of the prostate adenocarcinoma, missing prostatic involvement, and local recurrence in the prostate-sparing, the position of this surgery regarding oncological results is still under debate. However, the quality of life of these patients may be better than the standard cystectomy.

## CONCLUSION

Among various factors, only distance between the tumor and the bladder neck had a significant predictive value on the prostatic involvement. Although vascular invasion may increase the risk of invasion, but in comparison with the previous studies, tumor multifocality, grade, stage, and CIS do not show any obvious correlation with prostatic involvement in the bladder TCC.<sup>(24,25)</sup> Therefore, it is reasonable to avoid the prostate-sparing or capsule-sparing cystectomy in patients with the bladder tumors very close to the bladder neck. However, it does not mean that when the distance of the bladder tumor from the bladder neck is sufficient, we can perform this surgery properly, because further evaluations with a

larger group of patients may modify the final conclusion.

## CONFLICT OF INTEREST

None declared.

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