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# Pathologic assessment and clinical significance of prostatic involvement by transitional cell carcinoma and prostate cancer

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**Abstract**

The prostate is commonly involved by transitional cell carcinoma (TCC) in patients with bladder cancer. A number of clinicopathologic factors including multifocal carcinoma in situ, tumor location, and tumor stage are associated with prostatic TCC (pTCC). In addition, the manner and extent of pathologic examination also makes a significant difference in the detection rate. Distinct patterns and extent of pTCC have been described and are associated with pathologic stage of the primary bladder tumor as well as prognosis. Preoperative transurethral biopsy of the prostatic urethra is a sensitive and accurate method to detect pTCC and is helpful for surgical planning. Given the high incidence of pTCC and prostatic adenocarcinoma, radical cystoprostatectomy is the treatment of choice for loco-regional control for patients with T4a disease. Further studies are necessary to establish the role of neoadjuvant and adjuvant therapy for patient with prostatic stroma invasion. 

*Keywords:* Bladder cancer; Prostatic transitional cell carcinoma; Prostate adenocarcinoma; Guidelines

## Introduction

In-situ transitional cell carcinoma (TCC) of the prostate was first described over half a century ago and continues to be a puzzle regarding optimum strategy for diagnosis and management of prostatic TCC (pTCC) [1,2]. The prostate is involved with TCC in up to 48% of patients undergoing radical cystoprostatectomy for bladder cancer and may be the primary source of TCC in a small number (3%) of patients [3]. Several possible mechanisms have been proposed to explain the pathogenesis of pTCC: (1) synchronous neoplastic transformation of the bladder and prostatic urothelium. The prostatic urethral mucosa and large prostatic ducts that empty into the urethra are lined with the same transitional epithelium as that of the urinary bladder, and they are exposed to the same carcinogenic insult that is associated with a number of well established risk factors, including cigarette smoking and occupational exposure to bladder specific carcinogens; (2) pagetoid spread of TCC via the bladder neck. The proximity of the prostatic urethra and bladder neck facilitate spreading of in situ carcinoma cells in a pagetoid intraepithelial fashion. A high incidence of pTCC in patients with carcinoma in situ (CIS) in urinary bladder supports these two hypotheses. The association of pTCC with location of tumors at the bladder neck further supports pagetoid spread as a significant mechanism in some cases; (3) direct transmural invasion of the prostate by invasive bladder cancer either posteriorly through the extravesical tissue or directly through the bladder neck [4]; (4) implantation associated with shedding of TCC tumor cells from the urinary bladder or upper urinary tract [5]. The dominant mechanisms appear to be intraurethral (synchronous or pagetoid spread) while direct transmural invasion accounts for 10% to 26% of the invasive cases [6–9].

## Incidence and method of prostate pathologic evaluation

The incidence of prostatic involvement by TCC in patients with bladder cancer ranges from 16% to 48% [6,7,9–11]. The variable incidence relates to study design, patient population, sample size, methodology, and extent of pathologic examination of the prostate. Two important causes for this variation relate to the presence or absence of CIS in the urinary bladder and the manner of examining the prostate. The incidence of pTCC is highest in patients with bladder CIS, with a range of 46% to 80% [10,12,13].

It has also been demonstrated that a higher incidence of pTCC was detected if the prostate was examined by whole-

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Table 1
Comparison of the incidence of pTCC in radical cytoprostatectomy specimens by routine selective sections or whole-mount step sections of prostate

| Authors (year) | Type of prostate examination | No. cases | No. pTCC | % |
|---|---|---|---|---|
| Schellhammer et al. (1977) [16] | Routine | 350 | 41 | 12 |
| Hardeman et al. (1990) [14] | Routine | 86 | 30 | 35 |
| Esrig et al. (1996) [6] | Routine | 489 | 143 | 29 |
| Nixon et al. (2002) [15] | Routine | 192 | 30 | 15.6 |
| Total | Routine | 1117 | 244 | 21.8 |
| Wood et al. (1989) [10] | Whole mount | 84 | 36 | 43 |
| Reese et al. (1992) [17] | Whole mount | 115 | 33 | 29 |
| Revelo et al. (2004) [11] | Whole mount | 121 | 58 | 48 |
| Shen et al. (2006) [9] | Whole mount | 214 | 69 | 32.2 |
| Total | Whole mount | 534 | 196 | 36.7 |

Whole mount step section is more sensitive than routine selective section for detecting pTCC ($P < 0.001$).

mount step sections of the entire prostate rather than routine selective sections of prostate (Table 1). The incidence of pTCC ranged from 15.6% to 35% with an average of 21.8% in larger series when the prostates were examined by routine selective sections [6,14–16]. However, in 4 studies including ours that utilized whole-mount section analysis, the incidence of pTCC ranged from 32% to 48%, with an average of 36.7% ($P < 0.001$) [9–11,17]. Whole-mount step sections of the entire prostate at 4 to 5 mm intervals appear to provide the most accurate means available for determining the presence or absence of transitional cell carcinoma of prostate. These studies strongly suggest that pTCC will be under-reported with standard selective sectioning. A whole-mount step section analysis or more extended sections of prostate from radical cystoprostatectomy specimens should be obtained from patients with CIS of the bladder or when pTCC is detected preoperatively.

Transurethral biopsy may also affect the detection of pTCC on the final pathologic cystoprostatectomy specimen. Precystectomy urethral biopsy or resection and fulguration may eliminate or destroy the superficial prostatic urothelial CIS. Wood et al. noted that 5 of 34 patients (14.7%) with a precystectomy prostatic urethral biopsy positive for pTCC, demonstrated no residual tumor in the prostate on review of the cytoprostatectomy specimens [10]. We have shown similar findings in that 11 of 50 patients (22%) with pTCC on the prostatic urethral biopsy had no pTCC identified in whole-mount sections of the entire prostate; 10 of 11 of these patients had CIS only on the biopsy of prostatic urethra [18].

Several studies have addressed the predictors of occurrence of pTCC, including multifocal bladder papillary tumor or CIS, location of tumor at trigone or bladder neck, and advanced stages of bladder cancer [10,11,15,19,20]. Two of the major determining factors for intraurethral pTCC are multifocality of urothelial carcinoma, particularly CIS, and tumor location at trigone or bladder neck. High bladder tumor stage, in contrast, is probably more closely associated with extravesical penetrating invasion of prostate from bladder cancer.

## Patterns of prostatic TCC

Schellhammer et al. first described in detail 3 microscopic patterns of prostatic involvement by TCC, i.e., ductal only, ductal/acinar involvement with, or without, stromal invasion, and showed that noninvasive in-situ prostatic patterns are usually associated with low stage bladder tumor and better 5-year survival [16]. Since then, several studies have confirmed the importance of recognizing in situ carcinoma and distinguishing it from stromal invasion [6,9,21–24].

We studied 214 men who underwent RC and had whole-mount step section analysis of the prostate [9]. Risk factors for pTCC included bladder CIS (both focal and multifocal) and lymph node metastases. We observed 5 distinct patterns: (1) CIS of the urethra or prostatic ducts/acini; (2) superficial invasion of the prostatic stroma (equivalent to lamina propria (LP) invasion of the bladder); (3) deeper invasion into the stroma extending from CIS of the urethra and/or ducts and acini; (4) periprostatic soft tissue invasion of TCC arising from the bladder; and (5) invasion of prostate via transmural penetration of bladder cancer (Fig. 1). Of the 69 patients with pTCC, 30 had only CIS of the urethra [6], urethra/ducts [14], or ducts and acini [10]. The stromal invasive pTCCs included lamina propria invasion [11], deep stroma invasion [13], periprostatic/SV invasion [5], or direct penetration from the bladder [10]. pTCC was associated with a higher risk of lymph node metastasis and advanced pathologic stage of the bladder tumor. There was a statistically significant difference in 5-year survival for patients with no pTCC compared with patients with CIS or LP involvement only and patients with established stroma invasion who had the worst 5-year survival. pTCC retained significance for survival after stratifying for lymph node status.

## Prognosis and staging

Schellhammer and associates were the first to show that prostatic involvement with stromal invasion significantly impacted survival [16]. In subsequent studies, the five-year survival rates ranged from 50% to 100% for patients with prostatic urothelial carcinoma in situ alone and 20% to 65% for patients with prostatic stromal invasion independent of bladder tumor stage [6,9,21–27]. Prostatic stromal invasion, regardless of mechanism, is staged as pT4a, while stage is determined solely by the bladder tumor stage in patients with CIS of the prostatic urethra, ducts, and/or acini only [28]. Within pT4a stage, no distinction is made between transmural penetrating invasion and invasion by intraurethral spread. Some studies, though, have suggested that transmural penetrating invasion of bladder cancer is asso-