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Original contribution

# Urothelial carcinoma of the bladder with transmural and direct prostatic stromal invasion: does extent of stromal invasion significantly impact patient outcome?

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**Summary** Urothelial carcinoma of the bladder with prostatic stromal invasion is included in stage pT4a of the new 2010 American Joint Committee on Cancer/Tumor-Node-Metastasis classification. Despite being a strong indicator of poor prognosis, there have been few large studies investigating the impact of extent of prostatic stromal invasion on patient outcome. A search of the surgical pathology and expert consultation files at our institution was made for cystoprostatectomy specimens diagnosed as urothelial carcinoma with prostatic stromal invasion from 2002 to 2009. Cases were further stratified as follows: group 1—focal prostatic stromal invasion and group 2—extensive prostatic stromal invasion. Only patients who had surgery as monotherapy and those with available follow-up information were selected for this study. Thirty-five cases of urothelial carcinoma with prostatic stromal invasion and follow-up information were identified. Mean patient age was 70 years (range, 44-88 years). Of these 35 patients, 15 (43%) had focal prostatic stromal invasion and 20 (57%) had extensive prostatic stromal invasion. Angiolymphatic invasion was identified in 93% of group 1 cases and 79% of group 2 cases. Positive margins were identified in 50% of group 1 cases and 45% of group 2 cases. Incidence of nodal metastasis was 64% for group 1 and 60% for group 2. Four (27%) of 15 cases in group 1 and 6 (30%) of 20 cases in group 2 had various histologic variants identified. In group 1, there were 2 cases of urothelial carcinoma with micropapillary features and urothelial carcinoma with focal squamous differentiation. In group 2, there were 3 cases of urothelial carcinoma with focal squamous differentiation, 2 cases of urothelial carcinoma with focal sarcomatoid differentiation, and 1 case of urothelial carcinoma with focal micropapillary features. One- and 3-year overall survival for group 1 was 53% and 27%, respectively. One- and 3-year overall survival for group 2 was 47% and 12%, respectively. Mean survival was 17.4 and 16.3 months for groups 1 and 2, respectively. Overall survival curves did not show a statistically significant difference between the 2 groups from initial diagnosis ($P = .889$) and radical cystoprostatectomy ($P = .369$). Our study suggests that extent of prostatic stromal invasion by urothelial carcinoma of the bladder as an independent factor does not impact overall patient survival. Other well-known prognostic factors including positive margin status, presence of aggressive histologic

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variants of urothelial carcinoma, angiolymphatic invasion, and distant metastasis likely play more critical roles in predicting outcome in male patients who have urothelial carcinoma with prostatic stromal invasion.


## 1. Introduction

The incidence of prostatic involvement by urothelial carcinoma (UCa) of the bladder ranges from 12% to 48% [1,2]. Schellhammer et al were the first to demonstrate that prostatic stromal invasion significantly impacted patient survival [2]. Subsequent studies have investigated the various mechanisms of prostatic stromal invasion, including direct transmural extension from the bladder, invasion from the prostatic urethra, and invasion from colonized prostatic ducts and acini [3-9]. Most studies suggest that the former carries a worse prognosis than the latter. Of note is the fact that the studies in the latter group often included cases of UCa in situ with colonization of normal/benign prostatic ducts and acini, without definite prostatic stromal invasion. Other studies have however demonstrated that, among patients with established deep prostatic stromal invasion, there is no difference in survival whether the prostatic stromal invasion occurred via transmural invasion of UCa of bladder origin or prostatic stromal invasion via the prostatic urethra, ducts, or acini [10]. UCa of the bladder with prostatic stromal invasion (direct invasion of the prostatic stroma following tumor extension beyond the muscularis propria/detrusor muscle) is designated as stage pT4a in the new 2010 American Joint Committee on Cancer/Tumor-Node-Metastasis classification, and UCa of prostatic urethral origin with prostatic stromal involvement is designated as pT2 [11]. However, UCa in situ of the prostatic urethra or colonization of prostatic ducts and acini without associated stromal invasion does not upgrade a tumor to pT2 or pT4a status. Some experts have questioned whether the extent (focal versus extensive) of prostatic stromal invasion is an independent prognostic indicator and if the pathologic stage of UCa of the bladder with transmural and direct prostatic stromal invasion (pT4a) should be further stratified based on the extent of prostatic stromal invasion. In this study, the largest to date addressing this issue, we examined 35 radical cystoprostatectomy specimens of UCa of the bladder with transmural invasion and direct prostatic stromal invasion to determine whether the extent of stromal invasion impacts patient outcome

## 2. Materials and methods

To accurately determine the "true significance" of extent (focal versus extensive) of prostatic stromal invasion in patients with UCa of the bladder, we were very selective with our patient population, only including those who had cystoprostatectomy as monotherapy. A search of the surgical pathology and consultation files at our institution was performed for patients who had cystoprostatectomy as monotherapy and were diagnosed as having UCa of the bladder with transmural and direct prostatic stromal invasion between 2002 and 2009. This study only applied to male patients, and only those with available follow-up information were selected. All slides were reexamined to determine extent of prostatic stromal invasion. *Stromal invasion* was defined as the presence of irregular urothelial nests or single cells in between benign prostatic glands, often eliciting stromal desmoplasia and a host inflammatory response in the absence of surrounding basal cells. Cases with prostatic stromal invasion from a prostatic urethral primary were excluded from the study. Cases were stratified as follows: group 1—focal prostatic stromal invasion and group 2—extensive prostatic stromal invasion. At present, there is no consensus regarding the definition of *focal* versus *extensive* prostatic stromal invasion. Although various quantification methods were initially used to distinguish focal versus extensive prostatic stromal invasion, including measurements in millimeters and percentage of involved surface area, there was still no significant difference in outcome; and thus, we chose the most reproducible approach (3 high-power fields on 1 slide) as a cutoff, which can be easily duplicated by practicing pathologists. Only cases with available follow-up information were selected for this study.

Overall survival (OS) was calculated both from time of diagnosis and from time of surgery to death or at the time this study was initiated and was estimated by the method of Kaplan and Meier. The survival status of the patient was censored if the patient was still alive at the cutoff date. Both point and 95% confidence interval (CI) estimates of OS survival probabilities at different time points (eg, 1, 2, or 3 years after diagnosis or surgery) were calculated. The log-rank test was used to test the difference in the OS between the 2 groups. The difference in categorical outcomes (such as angiolymphatic invasion [ALI], incidence of positive margins, incidence of nodal metastasis, and histologic variants) was compared with $\chi^2$ test or Fisher exact test.

This study was completed following the guidelines of and with approval from the Emory University Institutional Review Board.

## 3. Results

A total of 334 radical cystoprostatectomy cases were identified within the time frame of the study. Thirty-five