Does subclassification of pathologically organ-confined (pT2) prostate cancer provide prognostic discrimination of outcomes after radical prostatectomy?


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Does subclassification of pathologically organ-confined (pT2) prostate cancer provide prognostic discrimination of outcomes after radical prostatectomy?

Daniel P. Nguyen\textsuperscript{a,b}, Emily A. Vertosick\textsuperscript{c}, Vídit Sharma\textsuperscript{d}, Renato B. Corradi\textsuperscript{a,e}, Antoni Vilaseca\textsuperscript{a,f}, Toshikazu Takeda\textsuperscript{a,g}, Daniel D. Sjoberg\textsuperscript{c}, Nicole Benfante\textsuperscript{a}, Samson W. Fine\textsuperscript{h,i}, Victor E. Reuter\textsuperscript{h,i}, Peter T. Scardino\textsuperscript{a,i}, James A. Eastham\textsuperscript{a,i}, R. Jeffrey Karnes\textsuperscript{d}, Karim A. Touijer\textsuperscript{a,i,*}

\textsuperscript{a}Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
\textsuperscript{b}Department of Urology, University of Bern, Bern, Switzerland
\textsuperscript{c}Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA
\textsuperscript{d}Department of Urology, Mayo Clinic, Rochester, MN, USA
\textsuperscript{e}Mario Penna Cancer Institute, Belo Horizonte, Brazil
\textsuperscript{f}Urology Service, Hospital Clinic de Barcelona, Barcelona, Spain
\textsuperscript{g}Department of Urology, Keio University School of Medicine, Tokyo, Japan
\textsuperscript{h}Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
\textsuperscript{i}Weill Cornell Medical College, New York, NY, USA

*Corresponding author: Karim A. Touijer, MD
Urology Service, Department of Surgery
Memorial Sloan Kettering Cancer Center
353 East 68th Street, New York, NY 10065
E-mail: touijerk@mskcc.org
Phone number: 646-422-4486
Fax number: 212-988-0768
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Shortened running title: The impact of pT2 subclassification on outcomes post-prostatectomy

Keywords: death, metastasis, organ-confined, prostatectomy, prostate neoplasm, staging.
Abstract

Purpose: To test the latest update in the prostate cancer staging system by assessing prognostic association of pT2 subclassification with probabilities of survival-related outcomes in patients who underwent radical prostatectomy.

Patients and Methods: We retrospectively analyzed a total of 15,305 patients who underwent radical prostatectomy at two referral centers between 1985 and 2016 and had pT2 disease at final pathologic evaluation. Descriptive statistics compared baseline data stratified by pT2 substages (pT2a/b versus pT2c). Cox regression models adjusted for institution analyzed differences in rates of biochemical recurrence, metastasis, cancer-specific death, and overall mortality. Multivariable Cox regression models evaluated the predictive value of pT2 subclassification for survival, including the linear predictor from the Stephenson nomogram.

Results: Prostate-specific antigen levels and Gleason score differed significantly between pT2 substages (both p<0.0001). After median follow-up of 6.0 yr (interquartile range 3.3, 10.1), 2,083 patients had biochemical recurrence, 161 developed metastases, 43 died of prostate cancer, and 1,032 died from other causes. On univariate analysis, pT2 subclassification was significantly associated with biochemical recurrence (p=0.001) and distant metastasis (p=0.033) but not with cancer-specific death (p=0.6) or overall mortality (p=0.3). Multivariable analysis showed no evidence of a significant association between pT2 subclassification and biochemical recurrence (p=0.4) or distant metastasis (p=0.6); multivariable analysis was omitted for cancer-specific death and overall mortality due to lack of significance in univariate analysis.

Conclusions: Subclassification of pT2 prostate cancer is not a prognostic indicator of survival-related outcomes after radical prostatectomy. Our results validate the elimination of pT2 substages in the updated staging system.
1. Introduction

The purpose of a cancer staging system is to define patient groups whose outcome is more homogeneous within groups than between groups and to maximize prognostic accuracy. A higher stage should be associated with poorer outcomes. In the 8th (2017) edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, the tumor, node and metastasis (TNM) staging system eliminates subclassification of pathologic T2 (pT2) disease [1,2]. However, there was insufficient evidence whether pT2 subclassification has prognostic value in patients who undergo radical prostatectomy (RP) for clinically localized disease.

Previous studies have attempted to evaluate staging systems using biochemical recurrence (BCR) as an endpoint [3–7]. However, prostate-specific antigen (PSA) correlates poorly with survival outcomes [8–10].

The purpose of the current study was to validate the current staging system regarding organ-confined prostate cancer. Using data from two academic institutions to assemble the largest cohort of pT2 patients analyzed to date, we assessed the prognostic association of pT2 subclassification with the probability of BCR, distant metastasis, cancer-specific death and overall mortality in patients who underwent RP for clinically localized prostate cancer.

2. Patients and Methods

2.1. Patients

Prospectively collected data on 19,160 patients with pT2 disease at RP were retrospectively reviewed, following institutional review board approval (7,764 patients at Memorial Sloan Kettering Cancer Center [MSKCC] from 1985 to 2016 and 11,396 patients at...
Mayo Clinic from 1990 to 2012). In this cohort, RP had been performed by different surgeons, with routine pelvic lymph node dissection including removal of all lymphatic tissue along the external and internal iliac vessels and in the obturator fossa. Patients were excluded from our analysis if they were missing information on pT2 substage or staging system (N=478) or if they had metastatic disease at the time of surgery (N=36). In addition, to isolate the effect of stage and elude potential confounding due to adjuvant therapy effects on outcomes, patients were excluded if they had positive surgical margins (N=2,679), received neoadjuvant treatment (N=535), or had lymph node metastasis (N=127). The final study population consisted of 15,305 patients. All individual participants included in the study had provided informed consent.

2.2 Pathology

During the entire study period, RP specimens were processed as previously described for the respective institutions [11,12]. Briefly, specimens were inspected macroscopically, weighed, and dimensions recorded. At MSKCC from 1998 onward, the intact prostate and seminal vesicles were inked in two colors (right = green; left = blue) in the fresh state and the superficial fragments of muscular tissue surrounding the proximal urethra (i.e., bladder neck) were shaved. To permit assessment of the inked apical margin, the most apical 3 mm of the gland were sectioned and further segmented radially in a cone-like fashion, and embedded. The seminal vesicles were amputated at the junction with the prostate and submitted separately. Finally, the remaining bulk of the gland was sectioned from apex to base at approximately 3-mm intervals and entirely submitted as whole-mount sections for examination. At Mayo Clinic, RP specimens were processed using a systematic limited sampling protocol consisting of frozen sections initially followed by permanent section analysis the next day. At the time of the procedure, the apex and base were examined with multiple sections, and at least axial 8 sections were taken
through the remainder of the peripheral zone along with a section through each seminal vesicle (an average of 14 sections per specimen). All sections were then re-examined the next day using hematoxylin and eosin stained permanent sections. At both institutions, staging data according to the 2017 edition of the TNM staging system were available for primary tumor and lymph nodes [1,2]; the specimens had been re-classified as the TNM staging system evolved by reviewing pathology reports.

2.3 Oncologic outcomes

Follow-up protocol generally included serum PSA and physical examination at 6 wk, every 3-6 mo for 5 yr, and annually thereafter. Follow-up data were retrieved from institutional electronic databases.

For this analysis, BCR was defined as a single postoperative PSA $\geq 0.4$ ng/mL. A sensitivity analysis was performed with BCR defined as a PSA level $\geq 0.1$ ng/mL with confirmatory rise, using the MSKCC cohort. Recurrence information was based on clinical and radiologic findings, and metastasis was defined as the first evidence of distant relapse. Death due to prostate cancer vs. other cause was documented according to medical records or death certificates.

2.4 Statistical analyses

Wilcoxon rank-sum and Chi-square tests compared baseline data stratified by pT2 substages. Because in the Mayo Clinic database and part of the MSKCC database, pT2a and pT2b substages are grouped into the same category, and because the existence of pT2b disease is controversial [13], we decided to focus the analysis on pT2a/b (unilateral) versus T2c (bilateral)
disease. Cox proportional hazards models adjusted for institution were used to compare rates of
BCR, metastasis, death from disease and overall mortality between pT2a/b and pT2c patients.
When these Cox models yielded significant differences, the predictive value of pT2
subclassification on survival was evaluated in multivariable Cox regression models including the
linear predictor from the Stephenson nomogram [14] and institution. The Stephenson nomogram
was used to calculate a predicted risk of BCR based on preoperative PSA, post-RP Gleason
grade, extracapsular extension, seminal vesicle invasion, nodal status and surgical margin status.
Additionally, we included an interaction term between pT2 substage and institution to assess
whether associations differed based on institution. As we had data on surgeries done at Mayo
Clinic until 2012 but at MSKCC until 2016, we performed a sensitivity analysis which repeated
all analyses but only included surgeries up to the end of 2012. As an additional sensitivity
analysis, we repeated the analyses restricting the cohorts to all surgeries performed between 2007
and 2012 to include patients with modern grading only. We also repeated the main analyses
using clinical T2 substage instead of pathologic T2 stage. All p-values are two-sided with
statistical significance evaluated at the 0.05 alpha level. To assess the precision of the obtained
estimates, 95% confidence intervals (CI) were calculated. All analyses were performed using
Stata 13 (StataCorp, College Station, TX, United States).

3. Results
3.1. Baseline and pathologic data
For the entire cohort, median age was 61 (interquartile range [IQR] 56, 66) and median
serum PSA level was 5.2 (IQR 3.9, 7.2). There was a small but significant difference in median
PSA of 0.1 ng/ml between pT2a/b and pT2c disease (p<0.0001, Table 1). Approximately half of
pT2c patients had Gleason ≥7 disease, as compared to less than a third of pT2a/b patients (p<0.0001) (Table 1).

3.2. Oncologic outcomes

The median follow-up for living patients was 6.0 yr (IQR 3.3, 10.1). During follow-up, 2,083 patients had BCR, 161 developed metastases, 43 died of prostate cancer, and 1,032 died from other causes. After adjusting for institution, pT2 subclassification was significantly associated with BCR (p=0.001) and with distant metastasis (p=0.03). However, we found no evidence of an association with overall mortality or death from disease (p=0.3 and p=0.6, respectively). Cumulative incidence estimates are adjusted for institution and graphically depicted in Figures 1 to 4. Adjusted estimates at 10 yr are given in Table 2. When controlling for other prognostic factors, we found no significant association between pT2 subclassification and BCR (p=0.4) or distant metastasis (p=0.6) (Table 3). Sensitivity analyses using BCR as a PSA level ≥0.1 ng/mL with confirmatory rise were consistent with the main analysis (hazard ratio [HR] 1.29; 95% CI 0.97, 1.73; p=0.09). We found no evidence that the association between pT2 substage and outcomes differed by institution (data not shown).

As an additional sensitivity analysis, we repeated the analyses limiting the cohort to surgeries taking place up to December 31, 2012. All results were consistent with the main analyses, with bilateral disease having worse BCR rates when adjusting for institution only (p=0.001), but not when adjusting for other prognostic factors (HR 1.04; 95% CI 0.95, 1.14; p=0.4). There was also a significant association between pT2 subclassification and distant metastasis on univariate (p=0.037) but not on multivariable analysis (HR 1.09; 95% CI 0.77, 1.52; p=0.6), and no evidence of an association with cancer-specific death or overall mortality on univariate analysis (p=0.6 and p=0.3, respectively).
To account for modern grading, we also repeated these analyses including patients treated from 2007 to 2012 only. As in the main analyses, bilateral disease was associated with higher rates of BCR when adjusting for institution only (p=0.039), but not when controlling for other prognostic factors (HR 1.12, 95% CI 0.89, 1.40, p=0.4). In this cohort, we found no evidence of a difference in the rate of distant metastasis (p=0.6) or overall mortality (p=0.8) based on the presence of bilateral disease. Death from disease was not analyzed due to a limited number of events.

Among 4,827 patients who had clinical stage T2a, T2b or T2c disease, we found no evidence of an association between clinical T2 staging and BCR (p=0.1), distant metastasis (p=0.07), cancer-specific death (p=0.5) or overall mortality (p=0.6) on univariate analysis.

Discussion

The advent PSA-based screening led to early detection and a downward stage migration of prostate cancer. Nowadays, the majority of patients undergoing RP have organ-confined disease [15,16]. Repeated revisions of the AJCC/Union Internationale contre le cancer (UICC) TNM staging system have been undertaken since 1992, with the current 2017 system eliminating the three-tiered pT2 subclassification [1,2]. However, whether subclassification of pT2 prostate cancer adds prognostic value has not been robustly tested. Herein, we investigated the effects of using pT2 substages upon not only BCR, but also stronger endpoints. We found that pT2 subclassification does not add prognostic information for the outcomes of BCR, distant metastasis, cancer-specific death, or overall mortality.
Freedland et al observed no difference in BCR risk in patients with unilateral versus bilateral organ-confined prostate cancer at RP [3]. In two studies from Caso et al and Chun et al, respectively, comprising a total of 3716 patients, the three-tiered pT2 subclassification did not offer additional prognostic value compared to well-established risk factors for BCR [6,7]. Similar negative findings were reported in smaller series [4,5]. Our current analysis validates these results in a larger cohort with longer follow-up and more aggressive pathologic characteristics. For instance, compared to the analysis from Freedland et al where 81% of patients had pathologic Gleason score $\leq 6$ [3], this proportion was 55% in the current study. In the study from Chun et al, median follow-up was only 24 mo and 62% of patients had pathologic Gleason score $\leq 6$ [7].

There are, however, limitations in using BCR as an endpoint. The natural history of patients with PSA failure is variable and most patients will have an indolent clinical course [8–10]. In a study from Bianco et al, men with BCR had similar 1 yr probability of death from prostate cancer versus death from other causes (32% and 33%, respectively) [8]. At a median 9-yr follow-up in the Mayo Clinic cohort, BCR translated into clinical evidence of prostate cancer in 29% of patients and only 8% dying of prostate cancer [10]. Along the same lines, in the Johns Hopkins RP cohort, median survival had not been reached 16 yrs after first evidence of BCR [9]. Our study shows that rates of metastasis (1.6%) and cancer-specific death (0.4%) at 10 yr were relatively low in this pT2 population. These numbers are consistent with those from previous studies. In a cohort of 370 men with a median 9-yr follow-up after laparoscopic RP, 10-yr clinical progression–free survival rate was 97.3% for pT2 patients [17]. In a multicenter study from the United States including 11,521 patients who underwent RP, 15-yr prostate cancer–specific mortality risk was 0.8% to 1.5% for patients with pT2 disease [18]. These men
were more likely to die from competing causes. Similarly, two European studies with 10-yr follow-up reported 98% to 98.7% cancer-specific survival rates for patients with pT2 prostate cancer at RP [19,20]. Thus, pT2 cancer at RP represents a clinically homogeneous group of patients with an overall good prognosis.

Our results reinforce the concept that a field effect exists in prostate carcinogenesis, i.e. that multifocal prostate cancer foci arise independently within the prostatic tissue. Although the existence of the field effect in prostate cancer has been suggested for 20 years [21,22], more conclusive evidence has been recently reported [23,24]. Kosari et al’s found a common cancer transcriptome between benign prostate tissue adjacent to prostate cancer and unmatched prostate cancer, suggesting a wide field effect [24].

Our results validate the elimination of pT2 subclassification in the new AJCC/TNM staging system. Preoperative serum PSA level and pathologic Gleason grade remain the strongest prognostic factors in patients with margin-negative pT2 disease [3–7]. The rationale for pT2 subclassification had also been questioned from a biological perspective. First, is it appropriate that a single unilateral large tumor is assigned a lower pathologic stage than two small bilateral tumors [25]. Second, approximately 80% of prostate cancers are multifocal [4,13]. And third, it has been postulated that a true pT2b cancer, i.e., unilateral cancer occupying more than one-half of one lobe, may not exist. Eichelberger et al examined 369 totally embedded and serially sectioned whole-mount RP specimens. While 75% of these tumors were classified as pT2, not a single pT2b tumor was detected; a total of 312 cases (85%) were multifocal [13]. This controversial issue may explain the large variation of pT2b reporting among pathologists [25].

Looking ahead, a more informative grouping of pT2 disease may be based on size or volume of the index tumor, or percentage of gland occupied by tumor [26–28]. Wise et al reported that the
index tumor volume alone was an equally powerful predictor of prognosis as all tumor volume [28]. Thus, the index tumor volume may become a reliable predictor of outcomes after RP. However, no accepted standard technique of tumor volume measurement exists. Therefore, the prognostic value of the index tumor volume and other parameters remains uncertain.

Our analysis is subject to limitations inherent to retrospective studies, such as the possibility of uncaptured events after hospital discharge. To counterbalance that, regular correspondence took place with all patients who were not followed at the two institutions where the surgery was performed. Central pathologic review was not logistically feasible given the size of the cohort; however, assessment of RP specimens at both institutions was performed by highly experienced urologic pathologists. We could not take into account the shift in Gleason grading that has taken place since 2005 [29] and evolved into higher likelihood of higher grading being reported [30]. Furthermore, given the long natural history of prostate cancer, a median follow-up of 6 yrs may not be long enough to detect differences in outcomes. Finally, our data require validation in external datasets. These limitations notwithstanding, this is the first study that evaluates the effect of pT2 subclassification using robust survival endpoints in a large bi-institutional cohort allowing substantial statistical power.

## 4. Conclusions

In this bi-institutional cohort, subclassification of pT2 prostate cancer was not a prognostic indicator for BCR, the development of metastasis, death from prostate cancer or overall mortality. Our results validate the elimination of pT2 subclassification in the 2017 AJCC/TNM staging system.
Conflicts of interest: none.

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5. References


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multifocal prostate cancers in radical prostatectomy specimens. Urol 2002;60(2)264-9 n.d.

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Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma
2005;29:1228–42.


6. Figure legends

**Figure 1.** Cumulative incidence estimates for biochemical recurrence, adjusted for institution
only (top) and for institution and the Stephenson nomogram linear predictor (bottom). The blue
line represents pT2a/b disease and the red line represents pT2c disease.

**Figure 2.** Cumulative incidence estimates for distant metastasis, adjusted for institution only
(top) and for institution and the Stephenson nomogram linear predictor (bottom). The blue line
represents pT2a/b disease and the red line represents pT2c disease.
Figure 3. Cumulative incidence estimates for death from disease, adjusted for institution only (top) and for institution and the Stephenson nomogram linear predictor (bottom). The blue line represents pT2a/b disease and the red line represents pT2c disease.

Figure 4. Cumulative incidence estimates for overall mortality, adjusted for institution only (top) and for institution and the Stephenson nomogram linear predictor (bottom). The blue line represents pT2a/b disease and the red line represents pT2c disease.
**Table 1.** Patient and disease characteristics by pathologic T2 substage, N=15,305. Data are presented as frequency (%) or median (interquartile range).

<table>
<thead>
<tr>
<th></th>
<th>pT2a/b (N=5224)</th>
<th>pT2c (N=10,081)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (yr)</td>
<td>61 (56, 66)</td>
<td>61 (56, 66)</td>
<td>0.3</td>
</tr>
<tr>
<td>PSA (ng/mL) (N=15,124)</td>
<td>5.1 (3.6, 7.2)</td>
<td>5.2 (4.0, 7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pathologic grade group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>3571 (68%)</td>
<td>4910 (49%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Group 2</td>
<td>1190 (23%)</td>
<td>4065 (40%)</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>281 (5.4%)</td>
<td>780 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>99 (1.9%)</td>
<td>175 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Group 5</td>
<td>56 (1.1%)</td>
<td>108 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>27 (0.5%)</td>
<td>43 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>3384 (65%)</td>
<td>6667 (66%)</td>
<td>0.13</td>
</tr>
<tr>
<td>T2</td>
<td>1723 (33%)</td>
<td>3151 (31%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>42 (0.8%)</td>
<td>82 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>75 (1.4%)</td>
<td>181 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open RP</td>
<td>3835 (73%)</td>
<td>6457 (64%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Laparoscopic (non-robot-assisted) RP</td>
<td>352 (6.7%)</td>
<td>938 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>Robot-assisted RP</td>
<td>1037 (20%)</td>
<td>2686 (27%)</td>
<td></td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; RP: radical prostatectomy.
Table 2. Cumulative 10-yr incidence estimates with 95% confidence intervals by pathologic T2 substage for BCR, distant metastasis, prostate cancer death and overall mortality.

Estimates for BCR are adjusted for institution.

<table>
<thead>
<tr>
<th></th>
<th>pT2a/b</th>
<th>pT2c</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR</td>
<td>14.3% (13.1%, 15.6%)</td>
<td>16.6% (15.5%, 17.8%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>1.2% (0.9%, 1.7%)</td>
<td>1.8% (1.4%, 2.2%)</td>
</tr>
<tr>
<td>Prostate cancer death</td>
<td>0.3% (0.2%, 0.6%)</td>
<td>0.4% (0.2%, 0.6%)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>7.8% (6.9%, 8.7%)</td>
<td>8.3% (7.5%, 9.1%)</td>
</tr>
</tbody>
</table>

BCR, biochemical recurrence.
Table 3. Multivariable Cox regression models for the probability of BCR and distant metastasis (N=15,072). All models were adjusted for pathologic subclassification and the Stephenson nomogram linear predictor; the model for BCR was also adjusted for institution.

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>BCR</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>pT2a/b</td>
<td>Ref.</td>
<td>-</td>
</tr>
<tr>
<td>pT2c</td>
<td>1.04</td>
<td>0.95, 1.13</td>
</tr>
</tbody>
</table>

BCR, biochemical recurrence; CI, confidence interval; HR, hazard ratio.
Time from radical prostatectomy to death from prostate cancer, in years

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>pT2a/b 5224</th>
<th>3543</th>
<th>1720</th>
<th>493</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pT2c10081</td>
<td>5656</td>
<td>2318</td>
<td>559</td>
</tr>
</tbody>
</table>
Abbreviations and Acronyms:

AJCC = American Joint Committee on Cancer

BCR = biochemical recurrence

CI = confidence intervals

HR = hazard ratio

IQR = interquartile range

MSKCC = Memorial Sloan Kettering Cancer Center

PSA = prostate-specific antigen

pT2 = pathologic T2

RP = radical prostatectomy

TNM = tumor, node and metastasis