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Evaluation of the 7th American Joint Committee on Cancer TNM Staging System for Prostate Cancer in Point of Classification of Bladder Neck Invasion

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Objective: To assess the validity of the 7th edition of the American Joint Committee on Cancer TNM staging system for prostate cancer, paying special attention to bladder neck invasion, in an Asian population.
Methods: Clinicopathologic data of 368 men who underwent radical prostatectomy between 2003 and 2011 at our institution were reviewed. The main interest of this study was to confirm that both isolated positive bladder neck margin and positive bladder neck margin associated with other surgical margin have more favorable biochemical outcomes than seminal vesicle invasion (pT3b).
Results: The 3-year biochemical recurrence-free survival for men with organ confined disease, extraprostatic extension, isolated positive bladder neck margin, positive bladder neck margin with other surgical margin and seminal vesicle invasion was 88.9, 74.8, 51.2, 19.4 and 18.8%, respectively. On multivariate analysis, the increased risk of progression associated with an isolated positive bladder neck margin (hazard ratio 4.34, 95% confidence interval 1.40–13.46, $P = 0.011$) was less than that of seminal vesicle invasion (hazard ratio 9.67, 95% confidence interval 3.70–25.25, $P < 0.001$). As for the positive bladder neck margin with other surgical margin, the increased risk of progression (hazard ratio 9.32, 95% confidence interval 3.50–24.82, $P < 0.001$) was similar to that of men with seminal vesicle invasion.
Conclusions: In our study, men with isolated positive bladder neck margin and positive bladder neck margin plus other surgical margin had no worse biochemical outcomes than those with seminal vesicle invasion (pT3b). It is reasonable to classify prostate cancer with bladder neck invasion (the 6th American Joint Committee on Cancer edition pT4 category) into the 7th edition pT3 category.

Key words: prostatic neoplasms – prostatectomy – bladder – neoplasm staging

INTRODUCTION

Prostate cancer (Pca) is the most common cancer and the second leading cause of cancer death in men in the USA and Europe (1). In Korea, its rate of incidence has increased 20 times over the past two decades (2). Accurate and uniform staging for a tumor is vital for prediction of its behavior, treatment selection, evaluation of response to established and experimental treatments, and exchange of information and data among institutions. The American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) tumor, node and metastasis (TNM) staging system is one of the most commonly used staging systems. The TNM staging

system for Pca was first introduced in 1992 when the AJCC/UICC adopted a unified TNM staging system (3). Repeated revisions (4,5) have been undertaken in an effort to optimize prognostic accuracy.

The 2010 AJCC staging system (6), the new 7th edition, made several changes from the 2002 version (6th edition) in the staging of Pca. These changes included extraprostatic extension (EPE) and microscopic bladder neck (BN) invasion, both being included in the T3a category, Gleason score being recognized as the preferred grading system and the prognostic factors of Gleason score and preoperative prostate-specific antigen (PSA) being incorporated into stage grouping.

However, there is a paucity of literature investigating the validity of this change for Asian populations. Here, we aimed to assess the validity of the 7th edition of the AJCC TNM system for Pca, paying special attention to positive BN margin (+BN) (pT3a), in Korean men.

PATIENTS AND METHODS

We reviewed the medical records from a total of 379 patients who underwent radical prostatectomy (RP) under a diagnosis of Pca between July 2003 and April 2011 at our institution. Patients who received preoperative androgen deprivation or radiation therapy were excluded. Patients who had lymph node metastasis were excluded because they were at high risk for recurrence independent of RP specimen pathology. We also excluded men with unknown overall surgical margin (SM) status and men with known overall SM status but in whom the exact anatomical location(s) of the positive margins were unknown. This resulted in a final study population of 368 men. Pathological analysis of RP specimens was performed as previously described by True (7): prostates were inked along their surface area, and SMs were considered positive when carcinoma cells were seen to be in contact with the inked specimen surface. Tumor volume was determined using a visual estimation: The area of the tumor was measured in x and y diameters and multiplied by the depth, based on the presence of tumor in subsequent sections and the thickness of the sections. The sum total of all foci of tumor was the estimated tumor volume. Biochemical recurrence (BCR) was defined as a PSA of 0.2 ng/ml or greater after RP.

The main interest of this study was to confirm that +BN (both isolated +BN and +BN associated with at least one other +SM) after RP has a more favorable biochemical outcome than seminal vesicle (SV) invasion (pT3b). To compare BCR-free survival (BFS) among patients with an isolated +BN vs organ confined (OC) disease (pT2), EPE (pT3a), seminal vesicle (SV) involvement (pT3b) and +BN associated with other SM(s), the Kaplan–Meier method with the log-rank test was used. The multivariate Cox proportional hazards models predicting BFS were fit with preoperative PSA, pathological Gleason sum, tumor volume and pathological stage.

We also compared BFS according to the location of isolated positive margins, which were categorized as apical, BN or posterolateral using the Kaplan–Meier method. Additionally, we analyzed the prognostic implication of +BN compared with −BN, including analysis of whether patients with EPE or SV involvement had worse BFS when they had a +BN. All statistical analyses were performed using SPSS (version 15.0).

RESULTS

The medical records of a total of 368 patients were reviewed; 132 patients underwent open retropubic RP and 236 patients underwent robot-assisted RP. The mean ± SD follow-up in men without BCR was 24.7 ± 15.3 months (median 23). A total of 54 men (21.2%) experienced BCR. The clinical and pathologic features of patients are presented in Table 1. For 29 patients with pT2 disease, the distributions of positive margins were apex only ($n = 20$), BN only (4), posterolateral only ($n = 3$) and BN plus apex ($n = 2$). Table 2 shows the pathologic features of patients with +BN plus other SM(s).

Of the 368 men in this study, a +BN (which means 'positive BN margin', not the case with microscopic BN invasion with negative SM) was noted in 50 (13.5%). Of the 50 patients with a +BN, 8 had SV+ so they were included in the SV+ group, 22 had at least one other positive margin, leaving 20 men with an isolated +BN (a +BN without other SMs or SV+).

Table 1. Clinical and pathologic features of patients undergoing radical prostatectomy

Mean (SD)	
Age	63.5 (6.7)
PSA (ng/ml)	11.1 (11.9)
n (%)	
Clinical stage	
T1	87 (23.6)
T2/3	281 (76.4)
Pathologic Gleason score	
2–6	128 (34.8)
7	182 (49.5)
8–10	58 (15.7)
Surgical margins	
pT2 ($n = 143$)	29 (20.2)
pT3 ($n = 225$)	90 (40.0)
Pathological stage	
OC (EPE−, SV−)	143 (38.9)
EPE (SV−)	200 (54.3)
SV (EPE+/−)	25 (6.8)

SD, standard deviation; PSA, prostate-specific antigen; OC, organ confined; EPE, extraprostatic extension; SV, seminal vesicle.

Table 2. Pathologic features of patients with positive bladder neck margin plus other surgical margin(s)

SM status	BN+ apex ($n = 12$)	BN+ posterolateral ($n = 12$)	BN+ apex + posterolateral ($n = 4$)
PSA [mean (SD)]	19.1 (6.7)	30.6 (18.3)	26.5 (16.4)
Pathologic T stage [*n* (%)]			
pT2	3 (25)	1 (8.3)	1 (25)
pT3	9 (75)	11 (91.7)	3 (75)
Pathologic GS [*n* (%)]			
6	1 (8.3)	0 (0)	1 (25)
7	3 (25)	6 (50)	2 (50)
8–10	8 (66.7)	6 (50)	1 (25)

SM, surgical margin; BN, bladder neck; GS, Gleason score.

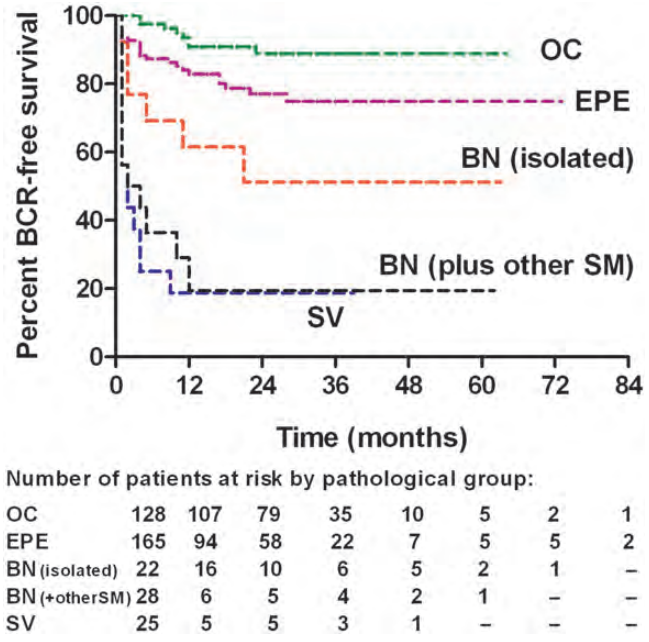

Figure 1. Kaplan–Meier curves of biochemical recurrence-free survival according to pathological groupings. OC, organ confined; EPE, extraprostatic extension; BN, bladder neck; SM, surgical margin; SV, seminal vesicle; BCR, biochemical recurrence.

The 3-year BFS for men with OC (EPE−, SV−) disease, EPE (SV−) and SV invasion was 88.9, 74.8 and 18.8%, respectively. For patients with an isolated +BN and +BN with other +SM, the 3-year BFS was 51.2 and 19.4%, respectively (Fig. 1). Of note, we observed that the BFS of men with an isolated +BN was significantly higher than that of men with SV involvement ($P = 0.017$). Men with a +BN with other +SM had a risk of recurrence that was most similar to that of men with SV+ ($P = 0.629$).

In proportional hazards models predicting BFS, preoperative PSA, pathological Gleason score of 8–10, EPE, SV invasion and +BN (isolated +BN and +BN with other +SM) were significant predictors of BFS. The multivariate analysis is detailed in Table 3. Multivariate analysis revealed that the increased risk of progression associated with an isolated +BN [hazard ratio (HR) 4.34, 95% confidence interval (CI) 1.40–13.46, $P = 0.011$] was less than that of SV+ (HR 9.67, 95% CI 3.70–25.25, $P < 0.001$). As for the +BN with other +SM, the increased risk of progression (HR 9.32, 95% CI 3.50–24.82, $P < 0.001$) was similar to that of men with SV+.

Table 3. Multivariate Cox proportional hazards regression analysis of factors predicting time to biochemical recurrence in men undergoing radical prostatectomy

	HR (95% CI)	*P* value
PSA (ng/ml)	1.025 (1.008–1.042)	0.004
Pathologic Gleason score		
2–6	Reference	
7	1.202 (0.599–2.410)	0.605
8–10	2.603 (1.213–5.584)	0.014
Tumor volume		
V1 (<1 cm^3)	Reference	
V2a (1–5 cm^3)	1.148 (0.369–3.892)	0.750
V2b (>5 cm^3)	2.410 (0.688–7.860)	0.198
Pathological grouping		
OC	Reference	
EPE	2.094 (1.190–4.015)	0.048
BN (isolated)	4.341 (1.400–13.461)	0.011
BN (plus other SM)	9.322 (3.501–24.823)	<0.001
SV	9.671 (3.704–25.250)	<0.001

HR, hazard ratio; CI, confidence interval.

When comparing the 3-year BFS according to the location of isolated +SM, we found no significant differences in BFS among the three (apical, posterolateral and BN) SM+ groups ($P = 0.114$). As for the prognostic implication of +BN compared with −BN, the +BN group had significantly higher incidence of adverse pathologic features (Table 4). When we compared BFS according to BN margin status (BN+ vs BN−), BFS of men with +BN was significantly lower than that of men with BN− ($P < 0.0001$, Fig. 2). Patients with EPE or SV invasion revealed a lower BFS when they had a +BN than when they did not (34.3 vs 79.3% at 3 years, $P < 0.001$ and 10.0 vs 37.5% at 3 years, $P = 0.21$, respectively).

DISCUSSION

In contemporary series, the prevalence of BN involvement after RP is 2.8–8.7% (8–10). The 1992, 1997 and 2002 AJCC TNM classification systems (3–5) classified Pca with

Table 4. Patient characteristics by the presence or absence of BN invasion

Characteristics	Bladder neck invasion		*P* value
	Absent	Present	
No. of patients	318	50	–
Mean age (SD)	63.9 (6.4)	62.1 (8.1)	0.306
Mean BMI (SD)	24.2 (2.3)	23.2 (1.9)	0.177
Mean PSA (SD)	8.6 (6.0)	26.6 (22.9)	<0.0001
No. of clinical stage (%)			
T1	76 (23.9)	12 (24.0)	0.987[a]
T2/3	242 (76.1)	38 (76.0)	
No. of pathologic Gleason score (%)			
2–6	118 (37.1)	10 (20.0)	<0.001[a]
7	159 (50.0)	24 (48.0)	
8–10	41 (12.9)	16 (32.0)	
No. of ECE (%)	186 (58.5)	38 (76.0)	0.018[a]
No. of positive SMs (%)	98 (30.8)	21 (42.0)	0.116[a]
No. of SV+ (%)	13 (4.1)	12 (24.0)	<0.0001[a]

BMI, body mass index.
[a]Chi-square test.

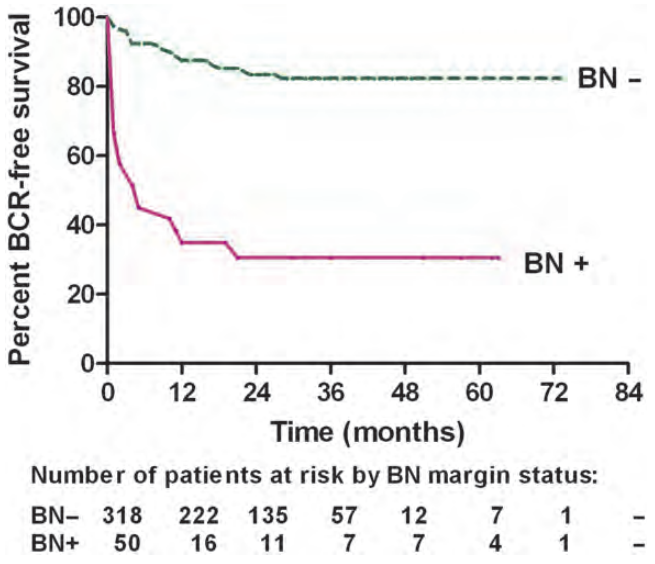

Figure 2. Kaplan–Meier curves of BCR-free survival according to BN margin status. BN, bladder neck; BCR, biochemical recurrence.

BN involvement within a unified pT4 category based on the extension of cancer into an adjacent organ. In the past, a designation of pT4 was clearly justified because most +SMs at the BN consisted of gross invasion of the bladder. Recently, however, the 7th edition of the AJCC TNM system (2010 AJCC) (6) changed the staging of Pca from its 2002 version and now includes microscopic BN invasion in the pT3a category. The classification changed because a +BN is more commonly noted as a microscopic focus on histopathological analysis in the current era of PSA screening and earlier Pca diagnosis. We aimed to investigate the validity of this change in Asian populations. To our knowledge, this is the first report regarding this issue in the Asian urologic field.

As is well known, multiple recent studies (8–14) demonstrated that the risk of biochemical progression associated with a +BN is more consistent with pT3 than with pT4. For instance, Yossepowitch et al. (13) expressed the need for downstaging of BN involvement in the 1997 TNM staging system, reporting that BN involvement in RP surgical specimens carried a lower risk of progression than SV invasion. Buschemeyer et al. (14) reported that a positive BN margin was associated with a risk of progression similar to that of SV invasion (T3b disease) when it was concomitant with other positive margins. They also demonstrated that the risk of recurrence for an isolated +BN might be closest to that of a pT3a lesion. Consistent with previous reports, our results also showed that the risk of recurrence of a +BN (both isolated +BN and +BN associated with other +SMs) was no worse than that of SV+ (pT3b).

Despite the apparent consensus that +BNs do not warrant a pT4 designation, the prognostic significance of a +BN relative to other +SMs is still inconclusive (8,15–19). For instance, Obek et al. (8) conducted a site-specific pathologic analysis of +SMs and reported that a +BN was the most significant adverse prognostic indicator and that it had three times the risk of BCR of an apical SM+. However, a 3-year follow-up study with more patients at the same institution revealed that BCR was not dictated by the specific location of the +SM (17). Similarly, others (9,13,20) found that a +BN was not associated with any greater risk of recurrence than other +SMs. Also in the current study, we found no significant differences in BFS among the three (apical, posterolateral and BN) +SM groups ($P = 0.114$).

As for another aspect regarding the prognostic implication of +BN, numerous prior studies (8–10,12,14) demonstrated that +BN accompanies other adverse pathological features such as higher rates of EPE, SV involvement and +SMs, a higher PSA and a greater pathological Gleason sum. Our series also corroborates prior evidence: 50 patients who had +BN in our study showed higher rates of ECE, other +SM, SV invasion and worse BFR when compared with the −BN group (Table 4, Fig. 2). Additionally, when we analyzed whether men with EPE or SV involvement had worse BFS when they had a +BN, both EPE and SV involvement group *with* +BN showed worse BFS than those *without* +BN (34.3 vs 79.3% at 3 years, $P < 0.001$ and 10.0 vs 37.5% at 3 years, $P = 0.21$, respectively). This finding was similar to that of a previous report (21).

Finally, we observed that men with isolated +BN (and SV−) showed much higher BFS than those with +BN plus other +SM (and SV−) (Fig. 1, Table 3). Regarding this result, we fully agree with Buschemeyer et al. (14) who suggested a hypothesis that an isolated +BN may be analogous to capsular incision due to a less than ideal operation,

whereas +BN plus other +SM may be due to advanced disease and aggressive tumor biology.

The present study had several limitations. First, this study was conducted retrospectively at a single institution, and the study sample was relatively small. Second, we did not include information on pelvic lymph node dissection (due to small number) and Pca-specific survival data. Third, pathological determination of +BN was not done under central review and a positive SM at the BN proper and at the base of the prostate may have been investigated together, although we think that this limitation does not diminish the significant message of this article. We believe that our study presents important preliminary results to assess the validity of the recent change in PCa staging in the AJCC 2010 staging system, in the Asian urologic field.

In conclusion, the present study demonstrates that it is reasonable to classify Pca with BN invasion (the 6th AJCC edition pT4 category) into the 7th edition pT3 category. Further large-scale, multi-center studies are needed to confirm our findings with increased statistical power.

Conflict of interest statement

None declared.

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