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ASSESSMENT OF THE AMERICAN JOINT COMMITTEE ON CANCER STAGING (6th AND 7th EDITIONS) FOR CLINICALLY LOCALIZED PROSTATE CANCER TREATED WITH EXTERNAL BEAM RADIOTHERAPY AND COMPARISON TO THE NATIONAL COMPREHENSIVE CANCER NETWORK RISK STRATIFICATION METHOD

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Abstract

BACKGROUND—To compare the prognostic value of the American Joint Cancer Committee (AJCC) staging version 6, version 7, and the risk-stratification model of the National Comprehensive Cancer Network (NCCN).

METHODS—Two-thousand four hundred twenty-nine men who received definitive RT with or without ADT (median follow-up: 74 months) were analyzed.

RESULTS—There was a migration of stage II patients to stage I with AJCC v7 (Stage I increased from 1% to 38%, while Stage II decreased from 91% to 55%). One (4%) pair-wise comparison of Kaplan-Meier estimates of biochemical failure, distant metastasis, prostate cancer specific survival, and overall survival between stages were statistically significant for AJCC v6. On the other hand, 16/24 (67%) of comparisons were significant with AJCC v7. For NCCN, 9/12 (75%) of comparisons were significant. Concordance probability estimate (CPE) and standard error (SE) analysis showed uniform and significant improvement in the predictive power of AJCC v7 versus AJCC v6 for all outcomes. CPE±SE values for AJCC v6 versus AJCC v7 was .51±.009 vs .59±.02 for BF, .54±.02 vs. .70±.05 for DM, .57±.009 vs. .76±.007 for PCSS, and .52±.006 vs. . 57±.01 for OS. CPE±SE values for NCCN was .59±.02 for BF, 0.72±.05 for DM, .80±.01 for PCSS, and .57±.01 for OS.

CONCLUSIONS—AJCC v7 is a major improvement over AJCC v6 because it better distributes patients among the stages and is more prognostic. The NCCN model is superior to the AJCC v7 and remains the preferred method for risk-based clinical management of prostate cancer with radiotherapy.

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Keywords

prostate cancer; staging; radiotherapy; American Joint Committee on Cancer (AJCC); The National Comprehensive Cancer Network (NCCN)

INTRODUCTION

The American Joint Committee on Cancer (AJCC) published the first edition of the *Cancer Staging Manual* in 1977. It used the T (tumor extent), N (lymph node invasion), and M (presence or absence of metastasis) to stage prostate cancer. Staging is important in order to: (1) categorize the severity of disease, (2) estimate prognosis, (3) recommend treatment, and (4) aid health care providers and researchers exchange information about patients.[1] The manual has been revised several times with the advent of new diagnostic tools and treatments.

There are several important changes that have been implemented in AJCC version 7 (AJCC v7).[2] For the first time, serum prostate specific antigen,[3] a predictor of survival is recognized in prostate cancer staging. Gleason score (GS) is now recognized as the preferred tumor grading system. And perhaps most importantly, PSA and GS are included in the stage grouping (i.e. I, II, III, and IV). Together, T-stage, PSA and GS have been commonly used in various risk group stratification models[4-7] that help physicians guide patients in terms of treatment and risks of recurrence, but they have not appeared together in the AJCC staging until now.

It is unclear however, whether these changes have significantly improved the staging system's ability to group patients according to prognosis. The purpose of this investigation is to compare the ability of AJCC v6[8] and AJCC v7[2] to predict biochemical failure (BF), distant metastasis (DM), prostate cancer specific survival (PCSS), and overall survival (OS) in men treated with radiotherapy (RT) with or without androgen deprivation therapy.[9]

MATERIALS AND METHODS

Between 1989 and 2006, 2,469 men with clinical stage T1-4, N0/X-N1, M0 adenocarcinoma of the prostate received definitive RT with or without adjuvant ADT. Three-dimensional-conformal RT (3D-CRT, July 1992 to June 2001) was used in 1,465 men (59%) and intensity modulated RT (IMRT, July 2001 to July 2004) was used in 1,004 men (41%). The mean follow-up time from completion of RT was 74 months (range: 1-213), 70 months (range: 2-108) for the IMRT group, and 86 months (range: 1-213) for the 3D-CRT group. The techniques used for 3D-CRT and IMRT have been previously reported.[10, 11]

Androgen deprivation therapy

ADT was generally used at the discretion of the treating physician, and consisted oral antiandrogen given for 1 to 4 months and a luteinizing hormone-releasing hormone agonist administered as depot injections.

Patient evaluation and staging

All patients had a history and physical exam including digital rectal exam (DRE), initial serum PSA (PSA), and histologic confirmation of adenocarcinoma with a GS. Thirty-one percent had a CT of the pelvis. Eighty-eight percent of the patients had a bone scan. T-category was established by palpation findings only, without upstaging using pathologic or radiographic information. Patients were staged using the AJCC v6[8] and v7[2] guidelines.

Statistical analysis

Univariate analysis was performed using a χ^2-test for discrete variables, and the Wilcoxon test was used for continuous variables. Kaplan-Meier estimation method and the Cox proportional hazard model were used to evaluate the ability of each clinical staging system to predict the time to BF, DM, PCSS, and OS. In the multivariate analysis (MVA), treatment (RT versus RT+ADT) and RT dose (< 75.6 Gy versus ≥ 75.6 Gy) effects were accounted for as covariates. The Benjamini & Hochberg adjustment[12] was used to produce a series of adjusted p-values. An adjusted p-value < 0.05 was considered significant. The BF was defined as the PSA nadir plus 2ng/mL.[13] The concordance probability estimate (CPE)[14, 15] and its standard error (SE) were used in assessing the predictive accuracy of the model for various endpoints. The closer the CPE is to 0.5, the lower the predictive accuracy of the model; the closer the CPE is to 1, the better the predictive accuracy.

RESULTS

Patient characteristics

Various patient- and treatment-related characteristics are listed in Table 1. Based on NCCN criteria, the proportion of patients with low-risk disease was 38%, intermediate-risk was 42%, and high-risk was 21%. The majority of patients, 79%, received RT alone (no ADT) to a median RT dose of 76 Gy. Of those men receiving ADT, the median duration was 11.2 months (range: 0.4 – 124).

Staging statistics

Patient staging statistics under AJCC v6 and v7 are listed in Table 2. When transitioning from AJCC v6 to v7, the proportion of men in stage I increased (1% to 38%), stage II decreased (91% to 55%), while stages III and IV remained the same (6% and 1%, respectively). Regarding the subdivision of stage II into A and B subcategories with AJCC v7, 35% of all patients had IIA disease and 20% had IIB disease.

Prognostic Value

Figure 1 illustrates KM estimates of BF (A), DM (B), PCSS (C), and OS (D) for AJCC v6 (left column) and AJCC v7 (right column). Table 3 shows the paired p-value comparison between any two KM curves from Figure 1. The significant (i.e. <0.05) paired p-values are bold-faced. In the AJCC v6 staging, overall differences in DM, PCSS, and OS were not significant, with the exception being the outcome prediction of PCSS for stage II and III patients. Contrarily, in the AJCC v7 staging, paired p-value comparisons were more likely to be significant. This is a marked improvement compared to AJCC v6. Figure 2 illustrates KM estimates of BF (A), DM (B), PCSS (C), and OS (D) for AJCC v7 stages IIA versus IIB. Substratification between stages IIA and IIB did not provide more prognostic information. Figure 3 illustrates KM estimates of BF (A), DM (B), PCSS (C), and OS (D) based on NCCN risk group. Table 4 shows the paired p-value comparison between any two KM curves from Figure 3. NCCN risk group stratification is significant for most of the KM curves in the outcome measures studies, particularly for OS.

Predictive accuracy

Table 5 lists the CPEs and SEs in evaluating the ability of the AJCC v6, v7, and NCCN risk groups to prognosticate BF, DM, PCSS, and OS after controlling for treatment and dose effects. The results show uniform improvement in the predictive power of the model based on AJCC v7 compared to that on AJCC v6 for all endpoints, in particular for DM and PCSS. NCCN risk group stratification is equally predictive of BF and OS, and it is more predictive of DM and PCSS. Figure 4 illustrates the data presented in Table 5.

DISCUSSION

Staging is important for radiotherapy because it guides treatment recommendations such the use ADT, radiation dose, and treatment volume (i.e. prostate only versus prostate and pelvis). While several relatively common models that subdivide patients into low-, medium-, and high- risk groups have been proposed,[16, 17] there have also been a number of models that are more sophisticated, but less commonly used.[5, 18-22] The results from these studies have been integrated in designing AJCC guidelines. We compared the ability of AJCC v6[8] and v7[2] to predict BF, DM, PCSS, and OS in men who received RT with or without ADT.

The first major improvement with AJCC v7 is better prognositication between stages I and II. According to AJCC v6, 2,263 (91%) men in our cohort were stage II with the great majority having T1c disease. Nine-hundred-eight (40%) of stage II patients migrated from AJCC v6 Stage II to AJCC v7 Stage I. The remaining 1,355 (60%) AJCC v6 Stage II patients remain Stage II. This migration positively influenced the prognostic value of the AJCC v7. Stage I patients had significantly longer times until BF, DM, and OS, when compared to AJCC v7 stage II patients (Table 3, Figure 1).

The second major advancement associated with AJCC v7 is the improved prognostic value and ability to predict for BF, DM, PCSS, and OS (Tables 3 and 5). The greatest gains were seen for DM and PCSS endpoints. For DM the CPE increased from 0.54 to 0.70 and for PCSS from 0.57 to 0.76. When considering that a CPE 0.5 is associated with purely random ranking, these improvements are a remarkable accomplishment that should be applauded.

These improvements are due to several important changes that distinguish the AJCC v7 from AJCC v6. First, PSA is recognized in TNM staging. Serum PSA is an important prognosticator in patients with a benign prostate exam,[23] and lower PSAs have been associated with more favorable pathological findings in clinical stage T1c cancers.[24] Second, the AJCC v7 TNM system obligates the GS to be used preferentially in assessing the histopathological tumor grade. The GS is an important determinant of outcome and has been found to be superior to other histopathological reports.[7, 25, 26]

Problems still exist with AJCC v7 staging. First, there are still too many “intermediate-risk” patients (i.e. stage II, 55%), and there is a lack of sub-stratification of these patients. The clustering of patients in stages I and II are likely secondary to the majority of patients presenting with localized or impalpable disease but an increased PSA.[27] Moreover, stage IIA patients do not have a statistically significant difference in rate of BF, DM, PCSS, or OS when compared to stage IIB patients (Figure 2). Second, AJCC v7 does not alter the number of patients in stages III and IV, a finding shown in other patient populations.[28] The proportion of patients in stage III was 6% and IV was 1%, which is small compared to stages I and II. Third, AJCC v7 does not have a high predictive accuracy for BF or OS (Table 5, CPEs 0.59 and 0.57, respectively). This is especially true for stratifying and predicting the outcomes of stage II and III patients (Figure 1, right column). Fourth, the NCCN risk groups have a statistically higher predictive accuracy compared to AJCC v7 for PCSS (Table 5, 0.8 vs. 0.76, respectively). Thus, the NCCN model is superior to the AJCC v7 and remains the preferred method for risk-based clinical management of prostate cancer with radiation therapy.

Clinical T-stage, GS, and initial PSA have been shown to be independent predictors of BF and are commonly used in staging systems.[16] The TNM staging system is a surgical staging system and does not include many other important pretreatment characteristics. Future models will use more advanced data analysis in predicting outcome. For example, to improve the TNM staging system, one may consider upstaging patients with low or favorable intermediate-risk disease and more than 50% positive core biopsies.[28-30] Second,

staging systems may include the number of GS 4 or 5 in biopsy specimens, as this value has been shown to be a predictor of BF and DM after RT, independent of GS.[31] Third, patients with a PSA velocity >2ng/mL in the year before radical prostatectomy or RT may be upstaged, as these men have been shown to have a lower PCSS.[32, 33]

Future systems may also integrate patient-specific biomarkers into prognostication. Patient- and disease-specific treatment is demanded by the U.S. government's impetus for expanding comparative effectiveness research (CER).[34] CER focuses to develop personalized medicine by examining the racial, ethnic, socioeconomic, and geographic variations in care that affect health outcomes.[35, 36] Prostate cancer is a high impact site of CER because of its high prevalence, the many treatment options available, and the emerging biomarkers used in its staging and treatment.[37]

The future of CER for prostate cancer therapy may integrate specific cancer- and patient-specific biomarkers into staging, including Bcl-2,[38-40] Bax,[38, 39] the Bcl-2/Bax ratio,[39, 41] CD-44,[42] e-cadherin,[42] p53,[42] p21/waf1,[41] COX-2,[43, 44] MDM2,[45] Ki-67,[46, 47] P120,[46] PCNA,[46] and DNA microarrays,[48] and p450 polymorphisms.[49] Thus, although the TNM staging system may be used to describe almost any patient with prostate cancer, its generalizability precludes its specificity and prognostic capability. Future biomarker-based staging systems, although not universal, may be more specific and have a greater predictive accuracy.

CONCLUSION

AJCC v7 is a major improvement over AJCC v6 because it better distributes patients among the stages and is more prognostic. Further improvements are needed as the majority of men (55%) are stage II and the sub-stratification into IIA and IIB was not prognostic. The NCCN model is superior to the AJCC v7 and remains the preferred method for risk-based clinical management of prostate cancer with radiation therapy.

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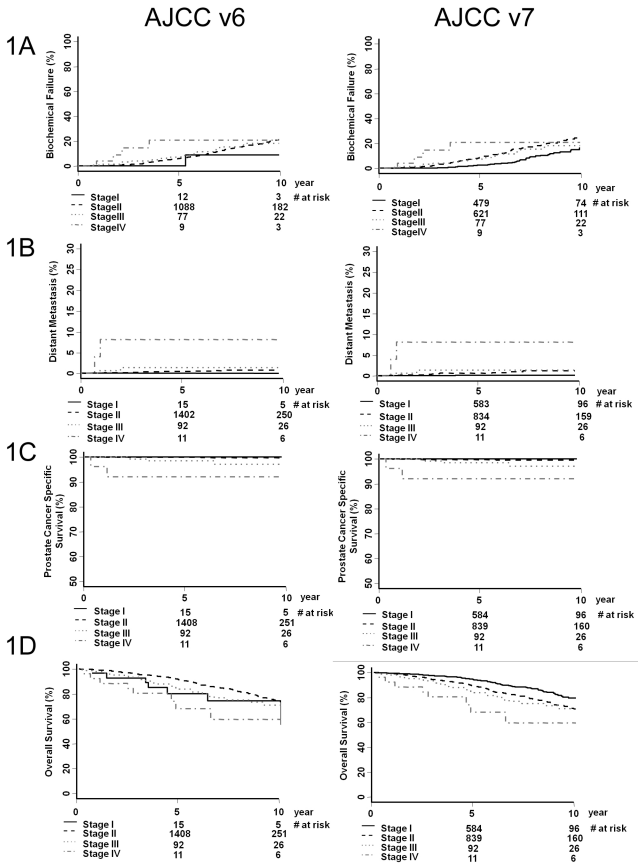

Figure 1.

Biochemical failure (A), overall survival (B), prostate cancer specific survival (C), and distant metastasis (D) by AJCC version 6 grouping (left column) and AJCC version 7 grouping (right column). The number of patients at risk is noted on the horizontal axes.

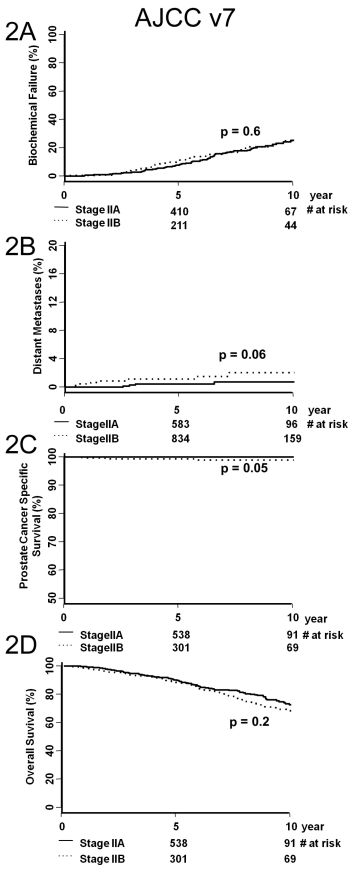

Figure 2.
Biochemical failure (A), overall survival (B), prostate cancer specific survival (C), and distant metastasis (D) of AJCC version 7 stage IIA and IIB patients.

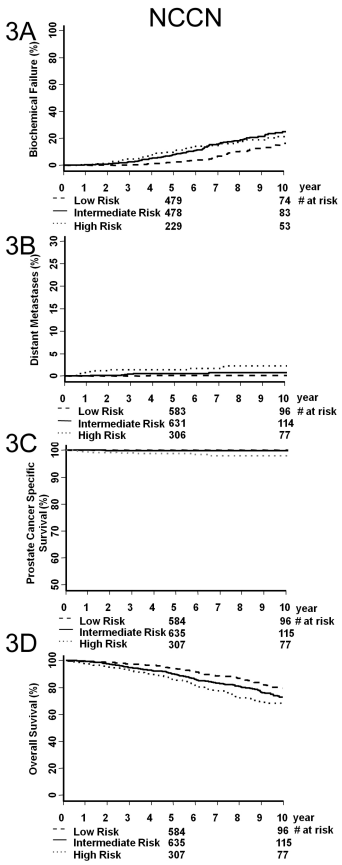

Figure 3.
Biochemical failure (A), overall survival (B), prostate cancer specific survival (C), and distant metastasis (D) of patients stratified by NCCN guidelines.

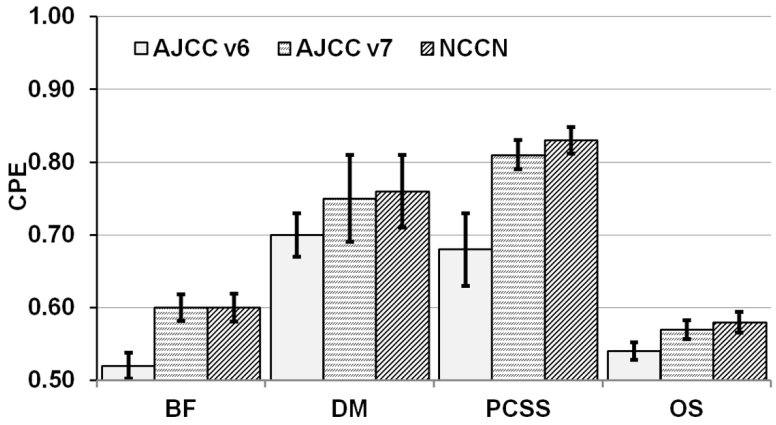

Figure 4.

The concordance probability estimates (CPEs) and their respective standard errors (SEs) in assessing the ability of the AJCC v6, v7, and NCCN risk groups to predict biochemical failure, distant metastasis, prostate cancer specific survival, and overall survival. Both treatment (RT versus RT+ADT) and RT dose (< 75.6 Gy versus ≥ 75.6 Gy) effects were included in the model as covariates. The closer the CPE is to 0.5, the lower the predictive accuracy of the model; the closer the CPE is to 1, the better the predictive accuracy. The results show uniform improvement in the predictive power of AJCC v7 and NCCN compared to that of AJCC v6 for all endpoints, in particular for DM and PCSS.

Table 1

Various patient and treatment related characteristics (n = 2,469).

Characteristic	# (%)
Age (y)	
mean	68
range	40 - 89
PSA (ng/mL)	
<10	1631 (66)
10-20	591 (23)
>20	247 (10)
Gleason score	
2-6	1608 (65)
7	627 (25)
8-10	234 (9)
ADT	
none	1941 (79)
<1 y	277 (11)
1-2y	75 (3)
> 2 y	176 (7)
Radiation dose (Gy)	
Median	76
Range	70 - 83
NCCN risk group	
low	938 (38)
intermediate	1012 (41)
high	518 (21)

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen

Table 2

Staging statistics under AJCC v6 and v7 guidelines.

AJCC v6	# (%)	AJCC v7	# (%)
Stage I	28 (1)	**Stage I**	936 (38)
T1a N0 M0 G1		T1a-c N0 M0 PSA<10 GS≤6	735
		T2a N0 M0 PSA<10 GS≤6	201
		T1-2a N0 M0 PSAX GX	0
Stage II	2263 (91)	**Stage II**	1355 (55)
T1a N0 M0 G2-4	5	Stage IIA	871
T1b N0 M0 Any G	19	T1a-c N0 M0 PSA<20 GS7	233
T1c N0 M0 Any G	1316	T1a-c N0 M0 PSA≥10 <20 GS≤6	224
T1 N0 M0 Any G	1344	T2a N0 M0 PSA≥10 <20 GS≤6	56
T2 N0 M0 Any G	947	T2a N0 M0 PSA<20 GS7	100
		T2b N0 M0 PSA<20 GS≤7	258
		T2b N0 M0 PSAX GX	0
		Stage IIB	484
		T2c N0 M0 Any PSA Any GS	134
		T1-2 N0 M0 PSA≥20 Any GS	171
		T1-2 N0 M0 Any PSA GS ≥8	179
Stage III	152 (6)	**Stage III**	152 (6)
T3 N0 M0 Any G		T3a-b N0 M0 Any PSA Any GS	
Stage IV	26 (1)	**Stage IV**	26 (1)
T4 N0 M0 Any G	13	T4 N0 M0 Any PSA Any GS	13
Any T N1 M0 Any G	9	Any T N1 M0 Any PSA Any GS	10
Any T4 Any N M1 Any G	1	Any T4 Any N M1 Any PSA Any GS	3

Abbreviations: AJCC = American Joint Committee on Cancer; T = tumor; N = node; M = metastasis; G = grade; GS = Gleason score; G1 = well differentiated (GS 2-4), G2-4 = moderately differentiated (GS5-6), G5-6; poorly differentiated (GS7-10); PSA = prostate specific antigen; v6 = 6th edition; v7 = 7th edition

Table 3

Paired p-value comparison of stages as assessed by either AJCC v6 or v7.

Outcome measure	Pair comparison (stage vs. stage)		p-value	
			AJCC v6	AJCC v7
Biological failure	I	II	0.5	**<0.0001**
	I	III	0.5	0.12
	I	IV	0.22	**0.03**
	II	III	0.8	0.3
	II	IV	0.22	**0.03**
	III	IV	0.37	0.22
Distant metastases	I	II	0.8	**0.03**
	I	III	0.6	**0.02**
	I	IV	0.22	**<0.0001**
	II	III	0.37	0.5
	II	IV	0.22	**0.0003**
	III	IV	0.22	**0.06**
Prostate cancer specific survival	I	II	0.8	0.1
	I	III	0.5	**0.0001**
	I	IV	0.2	**<0.0001**
	II	III	**0.01**	**0.02**
	II	IV	0.2	**<0.0001**
	III	IV	0.2	0.1
Overall survival	I	II	0.48	**0.0001**
	I	III	0.8	**0.0027**
	I	IV	0.5	**0.0003**
	II	III	0.22	0.313
	II	IV	0.5	**0.02**
	III	IV	0.2	0.12

Abbreviations: AJCC = American Joint Committee on Cancer; v6 = 6th edition; v7 = 7th edition

Bold-faced print denotes p-values <0.05.

Table 4

Paired p-value comparison of risk groups as assessed by NCCN guidelines.

Outcome measure	Pair comparison (risk group vs. risk group)		p-value
Biological failure	low	intermediate	**<0.0001**
	low	high	**0.0001**
	intermediate	high	0.97
Distant metastases	low	intermediate	0.084
	low	high	**0.0007**
	intermediate	high	**0.04**
Prostate cancer specific survival	low	intermediate	0.2
	low	high	**0.0003**
	intermediate	high	**0.0034**
Overall survival	low	intermediate	**0.002**
	low	high	**<0.0001**
	intermediate	high	**0.01**

Abbreviations: NCCN = National Comprehensive Cancer Network

Bold-faced print denotes p-values <0.05.

Table 5

The CPEs and their respective SEs in AJCC v6, v7 and NCCN assessment.

	AJCC v6		AJCC v7		NCCN	
Outcome measure	**CPE**	**SE**	**CPE**	**SE**	**CPE**	**SE**
BF	0.52	0.018	0.60	0.018	0.60	0.019
DM	0.70	0.030	0.75	0.060	0.76	0.060
PCSS	0.68	0.050	0.81	0.020	0.83	0.018
OM	0.54	0.012	0.58	0.014	0.58	0.014

Abbreviations: AJCC = American Joint Committee on Cancer; BF = biochemical failure; CPE = concordance probability estimate; DM = ditant metastasis; NCCN = National Comprehensive Cancer Network, v6 = 6th edition, v7 = 7th edition; OM = overall mortality; PCSS = prostate cancer specific survival; SE = standard error;

Note: The closer the CPE to 1, the better the predictive power of the model; the closer the CPE to 0.5, the worse the predictive power.