Digital Rectal Examination Remains a Key Prognostic Tool for Prostate Cancer: A National Cancer Database Review

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ABSTRACT

Background: Prostate cancer clinical stage T2 (cT2) subclassifications, as determined by digital rectal examination (DRE), are a historic method of staging prostate cancer. However, given the potential discomfort associated with prostate examination and the wide availability of other prognostic tests, the necessity of DRE is uncertain. This study sought to determine the prognostic value of the prostate cancer cT2 subclassifications in a contemporary cohort of patients. **Methods:** The National Cancer Database was used to identify a cohort of men with high-risk clinical T2N0M0 prostate cancer treated with external-beam radiotherapy and androgen deprivation therapies ± surgery from 2004 to 2010. We assessed overall survival from a landmark time of 10 months using Kaplan-Meier and log-rank test analysis. A multivariate proportional hazards model was used to estimate the simultaneous effects of multiple factors, including cT2 subclassification and other well-established prognostic indicators of overall survival in prostate cancer. **Results:** A total of 5,291 men were included in the final analysis, with a median follow-up of 5.4 years. The cT2a, cT2b, and cT2c subclassifications demonstrated increasing hazard ratios of 1.00 (reference), 1.25 (95% CI, 1.07–1.45; P=.0046), and 1.43 (95% CI, 1.25–1.63; P<.0001), respectively, reflecting a higher probability of death with each incremental increase in cT2 subclassification. This finding was independent of other known prognostic variables on multivariate analysis. **Conclusions:** Results show that cT2 subclassifications had independent prognostic value in a large and contemporary cohort of men. cT2 classification remains an important, low-cost prognostic tool for men with prostatic adenocarcinoma. The clinical relevance of this test should be appreciated and accounted for by providers treating prostate adenocarcinoma.

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Background

Adenocarcinoma of the prostate is the leading noncutaneous cancer diagnosis and the second leading cause of cancer mortality for men in the United States.[1,2] Patient outcomes are highly variable, and therefore risk stratification is critical in personalizing treatment to individual risk profiles. Risk stratification systems for prostate cancer have evolved over the past decades. In 1956, Dr. Willet Whitmore introduced the first prostate cancer classification system, which was subsequently revised in 1975 by Dr. Hugh Jewett.[3] The Whitmore-Jewett system was succeeded by the TNM staging system for prostate cancer, first formulated in 1987 and implemented by the AJCC in the United States in 1992.[4,5]

Pathologic T2 (pT2) subclassifications have been shown to lack prognostic value.[6,7] Accordingly, the newest 8th edition of the AJCC Cancer Staging Manual condenses the previous pT2 subclassifications into a single classification, "T2: organ-confined," such that the pT2 category is no longer subclassified by extent of involvement or laterality.[8] In contrast, the clinical tumor staging system has changed little over the decades, despite many advances in other aspects of clinical evaluation and treatment of prostate cancer (Table 1).

Since the initial implementation of the prostate cancer TNM staging system in 1992, revisions have been published in the 5th through 8th editions of the AJCC Cancer staging Manual.[8,9] An effort was made in the 1997 edition to improve the T2 classification by merging tumors occupying less than half of one lobe and those confined to one lobe into a single T2a category,[9] thus labeling tumors confined to the prostate but involving both lobes as T2b. However, a series of 1,755 patients with clinical stage T2 (cT2) prostate cancer treated with radical prostatectomy subsequently demonstrated on multivariate analysis that the 1992 but not the 1997 classification was prognostic for recurrence-free survival.[10] The revision was thus reversed in the 2002 edition and has remained unchanged.[9]

Minimal data are available in the modern era regarding prognostic value of the prostate cancer cT2

Table 1. Comparison of Historical and Current Prostate Cancer Clinical T Classification

Whitmore-Jewett System[3]	TNM	1992 TNM System[4,5] (AJCC 4th Edition)	2016 TNM System[8] (AJCC 8th Edition)
A Clinically inapparent	T1	Clinically inapparent	Same as 4th ed
	T1a	Incidental histologic finding in ≤5% of tissue resected (eg, on TURP)	Same as 4th ed
	T1b	Incidental histologic finding in >5% of tissue resected (eg, on TURP)	Same as 4th ed
	T1c	Identified by needle biopsy (eg, because of elevated PSA level)	Same as 4th ed
B Clinically apparent, but localized within the prostate	T2	Tumor palpable or visible on TRUS that is confined within the prostate	Tumor palpable and confined within the prostate
	T2a	Involves half of a lobe or less	Same as 4th ed
	T2b	Involves more than half of a lobe but not both lobes	Same as 4th ed
	T2c	Involves both lobes	Same as 4th ed
C Clinically apparent with local extension outside the prostate	T3	Tumor extends through prostatic capsule	Tumor extends through prostatic capsule but is not fixed and does not invade adjacent structures
	T3a	Unilateral extracapsular extension	Extracapsular extension
	T3b	Bilateral extracapsular extension	Tumor invades seminal vesicles
	T3c	Tumor invades seminal vesicles	NA
	T4	NA	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
D Metastatic spread			

Abbreviations: NA, not applicable; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; TURP, transurethral resection of the prostate.

subclassifications, as determined by digital rectal examination (DRE). It is known that DRE has significant inter-examiner variability,[11] and patients often find DRE to be invasive and undesirable. Multiple publications have examined trends in DRE use, finding that it is an underused physical examination component and may no longer be considered part of the core curriculum at certain medical schools.[12–14] Investigation is therefore critical to establish the presence of prognostic value for this examination in contemporary patients with prostate cancer.

We sought to determine the prognostic value of the cT2 subclassifications (cT2a–c) in a large cohort of men with high-risk clinical T2N0M0 prostate cancer treated with curative intent. The high-risk population was selected for this study because the end point of interest available was overall survival (OS), and this cohort included a large number of patients with cT2 disease and a high event rate for the end point of interest. Our results demonstrated the prognostic significance of the cT2 staging classifications in a large, contemporary cohort of men treated for high-risk prostate cancer, with important clinical and cost-conscious implications for the role of DRE in an era of oncologic practice in which expensive diagnostic tests are increasingly available and physical examination may be declining.

Methods

Patients

The patient population in the current study was obtained from the prostate cancer Participant Use Data File (PUF) from the National Cancer Database (NCDB), which is a nationwide oncology outcomes database that captures roughly 70% of all newly diagnosed cancer cases in the United States by obtaining data from >1,500 accredited sites. The database is supported by the American College of Surgeons and the American Cancer Society. Data are collected and transmitted using standardized coding, with variables including patient demographics, detailed staging, type of treatment administered, and OS outcomes.[15]

The Medical College of Wisconsin was granted user status for the prostate cancer PUF, which includes all incident cases of prostate cancer reported to the NCDB from 2004 through 2010. PUFs are entirely deidentified,

HIPAA-compliant data files and are only available via an application process to investigators affiliated with accredited cancer programs.[15] Exempt status was obtained from the Medical College of Wisconsin Institutional Review Board for the current study because it did not meet criteria for human subject research.

There were 1,294,126 incident cases in the prostate PUF for 2004 through 2010. Of these, the subset of men with high-risk clinical T2N0M0 prostate cancer treated with curative-intent external-beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) ± surgery was extracted (Figure 1). Disease risk was defined based on the risk groups defined in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), wherein high-risk disease is defined by the presence of any of the following clinical factors at diagnosis: Gleason score >7, prostate-specific antigen (PSA) level >20 ng/mL, or clinical stage T3a–T4.[2] Curative-intent therapy was filtered for based on radiation dose thresholds. Patients outside the age range of 18 to 90 years were excluded. The high-risk population was selected for this study because the end point of interest available in the PUF was OS, and this cohort included a high number of patients with cT2 disease and a high event rate. The final study population included 5,291 patients.

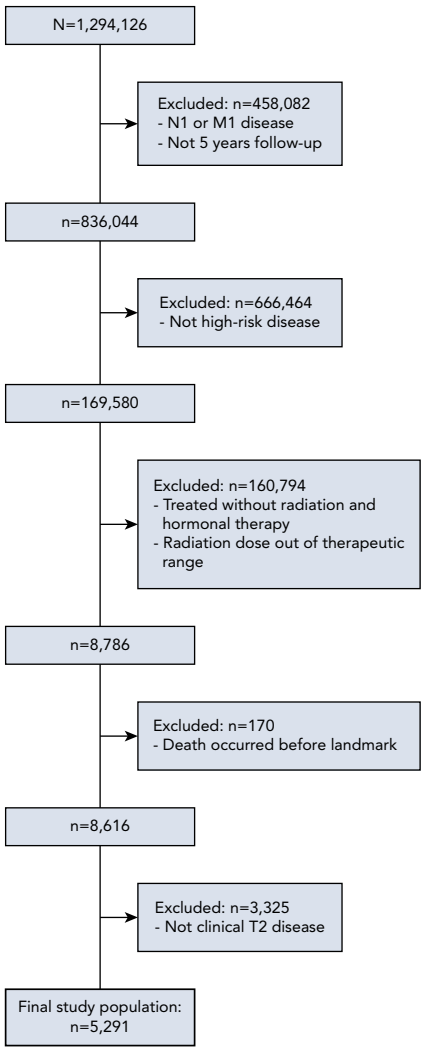

Figure 1. Patient selection.

Statistics

The NCDB database does not include treatment plans, and thus patients cannot be categorized into a treatment group at baseline. Therefore, landmark analysis was used with a landmark time of 10 months to adjust for the immortal time bias associated with the time to start of treatment; patients were classified into surgical treatment groups based on treatments received in the first 10 months after diagnosis. Treatment group classification was not changed based on later receipt of a treatment, and patients who died during the first 10 months were excluded from the analysis.

cT2 groups were compared using ANOVA/*t*, chi-square, and Kruskal-Wallis/Wilcoxon rank-sum tests for normally distributed, categorical, and ordinal outcomes, respectively. Exact versions of these tests were used when small cell sizes were present. Distribution assumptions were checked and nonparametric methods used where appropriate. In large datasets, tests of normality may be overly sensitive to small deviations. In these cases, we checked that the conclusions did not depend on an assumption of normality.

Single-predictor (bivariate) Cox proportional hazard models were used to estimate risk ratios for OS. We checked proportional hazards assumptions and found that Gleason score and PSA levels showed some deviation from proportionality. Model stratification was used to verify that the estimates and conclusions for other variables were not strongly influenced by nonproportional effects. Because these variables were not of primary interest, and the power to detect small variations was high in this dataset, we elected not to correct for these effects to simplify the analysis.

OS from the landmark time (10 months) was described using a Kaplan-Meier plot and log-rank test. A multivariate proportional hazards model was used to estimate the simultaneous effects of all factors considered. The final multivariable model included treatment, age group, race, insurance type, Charlson/Deyo comorbidity index (CDCI) score, PSA level at initial diagnosis (including a missing value group), Gleason score (including a missing value group), and cT2 subclassification. Because Gleason score was missing in

the NCDB data for more than half of the subjects, a post hoc sensitivity analysis of T2 staging interaction with Gleason missingness was performed.

All tests were 2-sided with a significance level of 0.05. The level-alpha approach for multiple comparisons was used, verifying overall significance before considering pairwise comparisons at the same alpha level. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc.).

Results

A total of 5,291 men with high-risk clinical T2N0M0 prostate cancer treated with EBRT and ADT ± surgery were included. Baseline patient demographics across the cT2 subclassifications are displayed in Table 2. A few demographic and clinical differences were noted among the different cT2 subclassification groups, supporting our controlling for these effects by including them subsequently in the multivariate model. Median age at diagnosis was 70 years (range, 38–90 years) for the entire cohort, with significantly younger age for men with higher cT2 subclassification ($P<.001$). Most patients were white (79%) and a minority were black (17%), with race not found to be associated with cT2 subclassification ($P=.126$). Patient medical insurance was primarily Medicare (62%) or private (29%), with private and Medicaid insurance being more common in men with a higher cT2 subclassification ($P<.001$). This was a generally healthy cohort, with a CDCI score of 0 in 88% of men, indicating no comorbid conditions recorded ($P=.415$).

Baseline tumor characteristics across cT2 subclassifications (Table 2) were typical for a high-risk cohort. Gleason score was ≤7 in 19.5% and >7 in 80.6% of patients for whom Gleason score data were available ($P=.064$). PSA level at diagnosis was <10 ng/mL in 15.7% of patients, 10 to 20 ng/mL in 7.0%, and >20 ng/mL in 76.8% ($P<.001$), with the *P* value indicating higher PSA level at diagnosis for men with a higher cT2 subclassification. There were 1,368 patients with the cT2a subclassification, 1,380 with cT2b, and 2,543 with cT2c. Treatment consisted of EBRT + ADT in 95.9% and surgery + EBRT + ADT in 4.1% ($P=.138$).

At a median follow-up of 5.4 years, there were 308 (22.5%), 355 (25.7%), and 757 deaths (29.8%) in the cT2a, cT2b, and cT2c groups, respectively. In the bivariate and multivariate analyses, the cT2a, cT2b, and cT2c subclassifications were found to have prognostic significance, with increasing HRs for the outcome of death (Tables 3 and 4). Multivariate values were 1.00 (reference), 1.25 (95% CI, 1.07–1.45; $P=.0046$), and 1.43 (95% CI, 1.25–1.63; $P<.0001$), respectively. This finding was independent of other known prognostic variables included in the multivariate model. Kaplan-Meier analysis also demonstrated statistical significance ($P<.0001$) of cT2 subclassification for OS (Figure 2).

Additional factors of prognostic significance for OS identified in the multivariate model included age group ($P<.0001$), insurance type ($P=.0037$), CDCI score ($P<.0001$), Gleason score ($P=.0182$), and PSA level at initial diagnosis ($P=.0040$). HRs and confidence intervals for these factors are listed in Table 4. For Gleason score subgroups, multivariate HRs were 1.00 for Gleason score 7 (reference), 0.72 for Gleason score ≤6 (95% CI, 0.31–1.68; $P=.4432$), 1.61 for Gleason score 8 to 10 (95% CI, 1.12–2.32; $P=.0107$), and 1.19 for Gleason score missing (95% CI, 0.88–1.61; $P=.2605$). On post hoc analysis of interaction between Gleason missingness and cT2 subclassification, no significant interaction was present ($P=.3796$; $df=2$). Factors assessed that did not meet the statistical significance threshold for OS on multivariate analysis were race ($P=.0907$) and treatment ($P=.3062$).

Discussion

Since its introduction in 1987, the TNM staging system for prostate cancer has changed little. pT2 subclassifications were recently revised in the 8th edition AJCC Cancer Staging Manual, because these had been shown to lack prognostic value.[6–8] Literature on the prognostic value of the cT2 subclassifications in a contemporary patient cohort is lacking. Risk stratification of prostate cancer is critical in guiding treatment decisions because prognoses can span a broad spectrum. A key component of the current NCCN risk stratification system is the clinical T stage as assessed by DRE,[2] and therefore it is important to establish the value of this parameter as a prognostic factor. Our study sought to evaluate the prognostic value of the prostate cancer cT2 subclassifications.

In the modern era, many advances have been made in the evaluation and treatment of prostate cancer. New biomarkers detected in urine are being evaluated in an effort to improve prostate cancer screening, including prostate cancer antigen 3 (PCA3) and *TMPRSS2-ERG* gene fusion.[16] The 4Kscore has gained popularity as a prognostic tool, incorporating testing of kallikrein blood biomarkers along with clinical factors, including findings on DRE.[17] Multiparametric MRI and MRI-guided prostate biopsy have become integral components of patient evaluation at many institutions.[18,19] Multiparametric MRI can be used to confirm low-risk disease before enrollment in active surveillance or to provide additional pretreatment information for patients with intermediate- to high-risk disease, and can help identify extracapsular extension and indicate aggressiveness of identified lesions.

In light of these new technically complex and expensive tests, it is particularly worthwhile to reevaluate traditional low-cost methods of disease assessment, such as DRE. Moreover, it is also prudent to investigate the

Table 2. Baseline Patient Characteristics

Characteristics	All Patients n (%)	cT2a n (%)	cT2b n (%)	cT2c n (%)	*P* Value
Age at diagnosis, y					
30–44	12 (0.2)	1 (0.1)	2 (0.1)	9 (0.4)	<.001[a]
45–59	756 (14.3)	150 (11.0)	209 (15.1)	397 (15.6)	
60–74	2,972 (56.2)	771 (56.4)	742 (53.8)	1,459 (57.4)	
75–90	1,551 (29.3)	446 (32.6)	427 (30.9)	678 (26.7)	
Median (range)	70 (38–90)	71 (41–88)	70 (41–90)	69 (38–90)	
Race					
White	4,180 (79.0)	1,106 (80.8)	1,100 (79.7)	1,974 (77.6)	.126[b]
Black	885 (16.7)	203 (14.8)	227 (16.4)	455 (17.9)	
Other	226 (4.3)	59 (4.3)	53 (3.8)	114 (4.5)	
Insurance type					
Private	1,550 (29.3)	379 (27.7)	381 (27.6)	790 (31.1)	<.001[b]
Medicaid	150 (2.8)	25 (1.8)	29 (2.1)	96 (3.8)	
Medicare	3,266 (61.7)	892 (65.2)	861 (62.4)	1,513 (59.5)	
Not insured	106 (2.0)	23 (1.7)	29 (2.1)	54 (2.1)	
Other government	130 (2.5)	24 (1.8)	47 (3.4)	59 (2.3)	
Unknown	89 (1.7)	25 (1.8)	33 (2.4)	31 (1.2)	
CDCI score					
0	4,643 (87.8)	1,211 (88.5)	1,221 (88.5)	2,211 (86.9)	.415[b]
1	538 (10.2)	134 (9.8)	129 (9.3)	275 (10.8)	
≥2	110 (2.1)	23 (1.7)	30 (2.2)	57 (2.2)	
Gleason score on biopsy					
≤6	59 (3.0)	20 (3.6)	11 (2.0)	28 (3.2)	.064[a]
7	328 (16.5)	81 (14.4)	92 (16.6)	155 (17.8)	
8	872 (43.9)	291 (51.8)	235 (42.4)	346 (39.7)	
9	669 (33.7)	157 (27.9)	200 (36.1)	312 (35.8)	
10	60 (3.0)	13 (2.3)	16 (2.9)	31 (3.6)	
Missing, n	3,303	806	826	1,671	
PSA level at initial diagnosis					
<10 ng/mL	831 (15.7)	286 (20.9)	255 (18.5)	290 (11.4)	<.001[b]
10–20 ng/mL	370 (7.0)	98 (7.2)	101 (7.3)	171 (6.7)	
>20 ng/mL	4,066 (76.8)	979 (71.6)	1,015 (73.6)	2,072 (81.5)	
Missing	24 (0.5)	5 (0.4)	9 (0.7)	10 (0.4)	
Treatment					
EBRT + ADT	5,072 (95.9)	1,324 (96.8)	1,318 (95.5)	2,430 (95.6)	.138[b]
Surgery + EBRT + ADT	219 (4.1)	44 (3.2)	62 (4.5)	113 (4.4)	

Abbreviations: ADT, androgen deprivation therapy; CDCI, Charlson/Deyo comorbidity index; cT2, clinical stage T2; EBRT, external-beam radiotherapy; PSA, prostate-specific antigen.
[a]Kruskal-Wallis test.
[b]Chi-square test.

utility and necessity of DRE, because patients often find it to be invasive and undesirable. Our series demonstrates that cT2 subclassification has statistically significant prognostic value for the outcome of OS. This finding was incrementally true for cT2a versus cT2b versus cT2c, and remained significant on multivariate analysis independent of other known prognostic variables, including PSA level and patient age, comorbidities, and race.

Our findings can be placed in the context of existing data that have supported current AJCC staging. In the

Table 3. Bivariate Factors for Overall Survival

Factors	HR (95% CI)	*P* Value	Overall *P* Value
Age at diagnosis, y			
30–44	Ref	NA	<.0001
45–59	1.03 (0.25–4.16)	.967	
60–74	1.53 (0.38–6.14)	.5473	
75–90	2.50 (0.62–10.03)	.1954	
Race			
White	Ref	NA	.0055
Black	0.81 (0.69–0.93)	.0041	
Other	0.78 (0.59–1.04)	.0921	
Insurance type			
Private	Ref	NA	<.0001
Medicaid	1.57 (1.14–2.17)	.0059	
Medicare	1.59 (1.40–1.81)	<.0001	
Not insured	0.65 (0.37–1.14)	.1306	
Other government	1.34 (0.92–1.95)	.1225	
Unknown	1.58 (1.07–2.35)	.0217	
CDCI score			
0	Ref	NA	<.0001
1	1.43 (1.22–1.67)	<.0001	
≥2	2.58 (1.95–3.40)	<.0001	
cT2 classification			
cT2a	Ref	NA	<.0001
cT2b	1.23 (1.06–1.44)	.0073	
cT2c	1.38 (1.21–1.57)	<.0001	
Gleason score on biopsy			
≤6	0.70 (0.30–1.63)	.404	.0325
7	Ref	NA	
8–10	1.37 (1.01–1.88)	.0464	
Missing	1.18 (0.87–1.60)	.2844	
PSA level at initial diagnosis			
<10 ng/mL	Ref	NA	.0111
10–20 ng/mL	1.52 (1.16–1.99)	.0026	
>20 ng/mL	1.06 (0.88–1.27)	.5522	
Treatment			
EBRT + ADT	Ref	NA	.0125
Surgery + EBRT + ADT	0.66 (0.48–0.92)	.0125	

Abbreviations: ADT, androgen deprivation therapy; CDCI, Charlson/Deyo comorbidity index; cT2, clinical stage T2; EBRT, external-beam radiotherapy; HR, hazard ratio; NA, not applicable; PSA, prostate-specific antigen.

1997 edition of the AJCC Cancer Staging Manual, tumors occupying less than half of one prostate lobe and those confined to one lobe were merged into a single T2a category. However, Cagiannos et al[10] reported on a series of 1,755 patients with cT2 prostate cancer treated with radical prostatectomy, demonstrating on multivariate analysis that the previous 1992 subclassification was prognostic for recurrence-free survival but the 1997 subclassification was not. Thus the cT2 subclassification was reversed in the 2002 edition and has remained unchanged.[9]

Demonstration of the prognostic significance of the cT2 subclassifications has important clinical and cost-effectiveness implications. In an era in which

Table 4. Multivariate Factors for Overall Survival

Factors	HR (95% CI)	*P* Value	Overall *P* Value
Age at diagnosis, y			
30–44	Ref	NA	<.0001
45–59	1.00 (0.25–4.04)	.9981	
60–74	1.34 (0.33–5.40)	.6797	
75–90	2.13 (0.53–8.59)	.2896	
Race			
White	Ref		.0907
Black	0.87 (0.75–1.02)		
Other	0.80 (0.60–1.07)		
Insurance type			
Private	Ref	NA	.0037
Medicaid	1.53 (1.10–2.12)	.0106	
Medicare	1.25 (1.08–1.44)	.0022	
Not insured	0.69 (0.40–1.21)	.1988	
Other government	1.28 (0.88–1.87)	.1926	
Unknown	1.46 (0.98–2.17)	.0602	
CDCI score			
0	Ref	NA	<.0001
1	1.44 (1.23–1.69)	<.0001	
≥2	2.77 (2.10–3.67)	<.0001	
cT2 classification			
cT2a	Ref	NA	<.0001
cT2b	1.25 (1.07–1.45)	.0046	
cT2c	1.43 (1.25–1.63)	<.0001	
Gleason score on biopsy			
≤6	0.72 (0.31–1.68)	.4432	.0182
7	Ref	NA	
8–10	1.61 (1.12–2.32)	.0107	
Missing	1.19 (0.88–1.61)	.2605	
PSA level at initial diagnosis			
<10 ng/mL	Ref	NA	.0040
10–20 ng/mL	1.54 (1.17–2.02)	.0018	
>20 ng/mL	1.52 (1.15–2.01)	.0031	
Treatment			
EBRT + ADT	Ref		.3062
Surgery + EBRT + ADT	0.84 (0.60–1.17)		

Abbreviations: ADT, androgen deprivation therapy; CDCI, Charlson/Deyo comorbidity index; cT2, clinical stage T2; EBRT, external-beam radiotherapy; HR, hazard ratio; NA, not applicable; PSA, prostate-specific antigen.

physicians have come to rely on new and expensive diagnostic tests, such as multiparametric MRI and genomic prognostics assessments, it is critical to highlight that traditional DRE remains a simple and valuable clinical tool for predicting prostate cancer outcome. Literature on how MRI compares with DRE for T2 subclassification is sparse, but MRI has been shown to outperform DRE in localization of cancer within the gland.[20] Data show that for clinical detection of T3 disease, subsequently confirmed on pathology, MRI has higher sensitivity than DRE; however, DRE has higher specificity.[21] Given the inexpensive, efficient, and widely available nature of DRE, we feel this physical examination component remains critical for

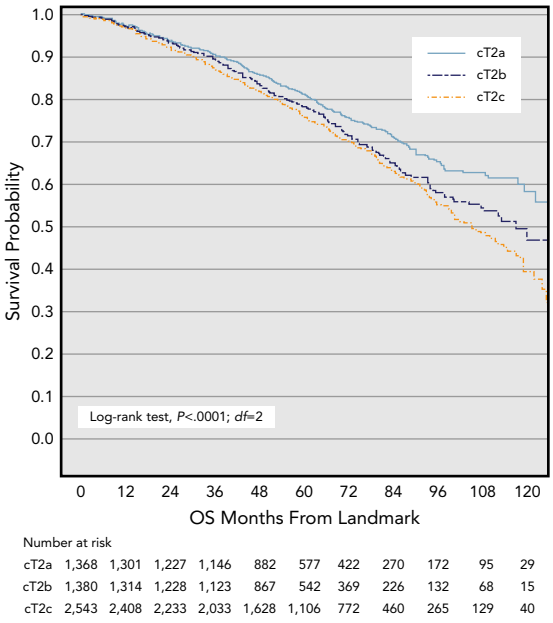

Figure 2. OS by cT2 classification.
Abbreviations: cT2, clinical T2; OS, overall survival.

oncologists to consider in evaluation of patients with prostate cancer.

Unfortunately, studies suggest that DRE is an underused component of the physical examination, and may not be emphasized as a critical skill in the training of future physicians.[12–14] We believe that DRE should continue to be performed and documented as a key component of the physical examination for all patients with prostate cancer and should be recognized as a low-cost prognostic tool for men with adenocarcinoma of the prostate. DRE also continues to have an important role in screening for prostate cancer, because abnormal findings in conjunction with abnormal PSA levels have been shown to increase detection of clinically significant prostate cancer.[22]

Our study has several limitations. Unfortunately, the NCDB prostate cancer data file does not contain data on biochemical failure, which would be another helpful prognostic end point to evaluate in addition to OS. However, OS may be the most clinically meaningful end point to correlate with the AJCC T2 classification. In addition, our study excluded low- and intermediate-risk cohorts. Given the relatively low incidence of T2 disease in these cohorts, it remains unknown whether our findings would hold statistical significance for all risk groups of patients with prostate cancer. As previously outlined, a further requirement for inclusion in this series was that radiotherapy be a component of treatment delivered, either upfront or postoperatively. Therefore, our results may not be as applicable to low- and intermediate-risk patients or those treated with surgery alone.

An additional limitation of this study was the absence of Gleason score data in a large number of NCDB subjects. We used several statistical strategies to evaluate any effect this might have had on the conclusions. Patients with a missing Gleason score were included in both the bivariate and multivariate models as an independent variable. This variable was not found to be a significant predictor of OS in either analysis. If a collection of patients with high Gleason score was somehow hidden in the "Gleason missing" cohort, we would expect that group to independently impact OS; such an influence on OS was clearly seen in the patients with a known Gleason score of 8 to 10.

An interaction test between Gleason missingness and cT2 subclassification was also performed and results were nonsignificant. If the presence of a missing Gleason score influenced the significance of clinical T stage on OS, we would have expected a statistically significant finding on the interaction test. Moreover, on multivariate analysis, the prognostic value of cT2 subclassification was highly significant and independent of the patients with Gleason score missing. Given our focus on an OS end point rather than a biochemical failure end point, any influence of missing Gleason scores should have been seen in this analysis. Despite missing Gleason scores, our data are sufficient to reasonably conclude that clinical T stage should be assessed routinely by oncologists for its potential prognostic significance.

Finally, it is possible that some patients may have been excluded from this analysis if they had a PSA level <20 ng/mL and Gleason score of 8 to 10 that was missing. In addition, the NCCN Guidelines define a "very-high risk category," characterized by primary Gleason pattern 5, >4 cores with Gleason score of 8 to 10, or T3b–T4.[2] We likely included some very-high risk patients in our analysis because we did not make an effort to exclude or uniquely identify these patients.

Our study has many noteworthy strengths. Most importantly, it involves a contemporary cohort of men, with cases reported from 2004 to 2010. These men are likely to have undergone a modern staging workup, including pelvic CT and bone scan, making the findings applicable to today's patients. Use of the NCDB data file allowed for evaluation of a large cohort of 5,291 high-risk men, making this the largest series to our knowledge to examine this question.

Next, the NCDB data represent a spectrum of clinical oncologic practice as opposed to a single major academic center or a group of major academic centers, and thus the conclusions are more applicable across a variety of clinical practices. Finally, the end point of OS is a

strength; it is often the main end point of interest in clinical practice and is less subject to misinterpretation than surrogate end points often used in prostate cancer, such as biochemical progression-free survival.

Our 5-year OS values were lower than those reported in a recent institutional series from a major academic center.[23] There are a number of reasons for this. First, we used a landmark time of 10 months after diagnosis from which to evaluate OS. Second, all men in the other series had undergone radical prostatectomy, whereas <5% in our series underwent treatment including radical prostatectomy. Thus, our cohort was likely a less healthy and higher-risk population in general. Third, single-institution data from a prestigious and accomplished academic center are unlikely to be reflective of outcomes seen in the NCDB, which encompasses a broad range of clinical practices and levels of oncologic expertise.

Another noteworthy finding is verification of previously established prostate cancer prognostic factors. Age, CDCI score, Gleason score, and initial PSA level have all been established as prognostic factors for OS in prostate cancer.[24,25] Our analysis contributes to this supporting body of data. Current literature is unclear as to the prognostic value of race and insurance type in prostate cancer.[26] We found insurance type but not race to be a statistically significant prognostic factor on multivariate analysis. However, this was not the focus of our study and warrants further study.

Conclusions

Results of our series demonstrate prognostic significance of the cT2 subclassifications as determined by DRE in a large, contemporary cohort of men treated for high-risk prostate cancer. In an era of resource-conscious oncologic practice, DRE remains an effective and low-cost prognostic tool in the management of men with adenocarcinoma of the prostate, and thus should be performed routinely by oncologists treating this malignancy.

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