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Minimal Impact of Clinical Stage on Prostate Cancer Prognosis Among Contemporary Patients With Clinically Localized Disease

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Abbreviations and Acronyms

AIC = Akaike information criterion
DRE = digital rectal examination
ECE = extracapsular extension
EPE = extraprostatic extension
PPB = percent of positive biopsy cores
PSA = prostate specific antigen
SVI = seminal vesicle invasion
TRUS = transrectal ultrasound

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Purpose: Clinical staging criteria for prostate cancer were established before the advent of widespread prostate specific antigen screening and extended biopsy templates. However, clinical stage remains commonly used in the modern era to predict prostate cancer outcomes. We hypothesize that in the context of data available from a contemporary biopsy, clinical stage no longer offers meaningful independent prognostic information for clinically localized prostate cancer.

Materials and Methods: We performed an analysis of men in the CaPSURE™ database with localized (clinical stage T1 or T2) prostate cancer who underwent radical prostatectomy. The usefulness of clinical stage and other clinical parameters (prostate specific antigen, biopsy Gleason score, percent of positive biopsy cores) to predict pathological outcomes and biochemical recurrence after radical prostatectomy was assessed using univariate and multivariable analyses.

Results: Of the 4,899 men in the study cohort 51.9% were classified as having T1 disease and 48.1% T2 disease. On univariate analysis clinical stages T2b and T2c were associated with pathological outcomes but only stage T2b was associated with biochemical recurrence. In contrast prostate specific antigen, biopsy Gleason score and percent of positive biopsy cores were strongly associated with recurrence and adverse pathological outcomes. On multivariable analysis clinical stage was of no use in determining pathological or biochemical outcomes.

Conclusions: In a multivariable model, including serum prostate specific antigen, biopsy Gleason score and percent of positive biopsy cores, clinical stage offered no independent information in predicting biochemical recurrence. The results of this study call into question the usefulness of clinical staging criteria in risk stratifying cases of localized prostate cancer treated with radical prostatectomy.

Key Words: prostatic neoplasms, neoplasm staging, prognosis, prostatectomy

THE clinical behavior of prostate cancer is widely heterogeneous. The natural history of the disease ranges from indolent to rapidly progressive and fatal. It is the responsibility of the practitioner to identify more aggressive tumors that warrant definitive treatment. Furthermore, it is important to predict those patients who are at risk for disease recurrence after local therapy.

No single clinical variable can predict outcome after treatment with sufficient accuracy. However, clinical staging criteria have traditionally been used to assist in the planning of treatment strategies and to make predictions concerning prognosis. The 2002 American Joint Committee on Cancer TNM clinical staging system for prostate cancer substratifies localized disease as T1 or T2.[1] Clinical T1

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disease is defined as a tumor neither palpable on DRE nor visible on TRUS. Clinical T2 disease includes lesions palpable on DRE or visible as hypoechoic lesions on TRUS, and is further subclassified as unilateral lesions involving less than 50% of 1 lobe (cT2a), unilateral lesions involving more than 50% of 1 lobe (cT2b), or lesions that are palpable or visible bilaterally (cT2c).

It has previously been shown that advanced clinical stage is associated with poor outcomes following radical prostatectomy.[2] In addition, numerous prognostic instruments have been developed which use clinical staging to assist in determining prognosis after surgery.[3–5] Some of these prognostic criteria rely heavily on clinical stage, weighting it as heavily as other potentially stronger clinical predictors such as biopsy Gleason score and pretreatment PSA.[6]

The widespread prevalence of PSA screening for prostate cancer has led to a significant migration toward lower stage, lower risk tumors.[7,8] As the majority of tumors encountered in today's practice are cT1c lesions, there is less stratification by clinical stage than had been seen in the past. Additionally, it has been shown that numerous clinical variables including pretreatment PSA, biopsy Gleason score and PPB are strong predictors of biochemical recurrence after radical prostatectomy, potentially stronger than clinical T stage.[3,5] Thus, we hypothesize that on multivariable analysis controlling for known clinical predictors of recurrence, clinical stage is of limited usefulness in predicting pathological outcomes and biochemical recurrence after radical prostatectomy for clinically organ confined disease.

MATERIALS AND METHODS

We performed an analysis of the CaPSURE database, a national disease registry of men with prostate adenocarcinoma recruited from 40 academic and community based urology practices across the United States. The database includes demographic, clinical, quality of life and resource use variables which have been recorded prospectively since 1997. Data for men diagnosed before 1997 were recorded retrospectively. Informed consent was obtained from each patient under institutional review board supervision. The accuracy of these data is ensured by a biannual random sample medical record review. Patients are treated according to physician usual practice patterns and are followed until death or study withdrawal. Participating clinicians directly report clinical stage to the database managers. Details of the database methodology have been published previously.[9]

Our analysis included patients in the CaPSURE database with cT1c or cT2 disease who underwent radical prostatectomy as primary treatment. Patients treated with adjuvant androgen deprivation or radiation therapy were excluded from the analysis. A separate analysis was performed without the exclusion of these patients to ensure that the results remained consistent.

Logistic regression was used to assess the associations of clinical variables with pathological outcomes (EPE, positive surgical margins and SVI). Individual models were run for each clinical variable of clinical stage (cT1c, cT2a, cT2b, cT2c), pretreatment PSA (0 to 10, 11 to 20, 21 to 30, greater than 30 ng/ml), PPB (0 to 10%, 11% to 33%, 34% to 50%, 51% to 75%, greater than 75%) and biopsy Gleason score (3 + 3 or less, 3 + 4, 4 + 3, 8 or greater). The lowest risk group was used as the reference for comparison. Multivariable Cox proportional hazards regression was used to determine the association of each clinical variable with biochemical recurrence (defined as PSA greater than 0.2 ng/ml on 2 measurements or any secondary treatment at least 6 months following surgery).[10] In calculating the hazard ratio we controlled for each of the clinical variables as well as the year of diagnosis. Separate models were run with PSA as a continuous and log-transformed variable as opposed to a categorical variable. As an additional test of the value of clinical stage, the full model including clinical stage was compared to a Cox model including all predictor variables except stage. The AIC was calculated for each model and these were compared with the likelihood ratio test. Finally a separate analysis comparing all cT1 to all cT2 tumors was performed to ensure that our results did not change when the subclassifications within T-stage were removed. All statistical tests were 2-sided and analyses were performed using Stata® version 10.1.

RESULTS

A total of 13,740 men were included in the CaPSURE registry. Of these men 6,036 underwent primary radical prostatectomy, and 359 had nonlocalized disease and were excluded from study, as were 150 diagnosed before 1990, 14 with cT1a or cT1b tumors, and 614 who received neoadjuvant and/or adjuvant therapy. The remaining 4,899 patients comprised the study cohort. The cohort was split evenly between patients with cT1 lesions (51.9%) and cT2 lesions (48.1%), including cT2a, cT2b and cT2c lesions (table 1).

Patient demographic data are summarized in table 1. Mean patient age at diagnosis was 61.1 ± 6.9 years. More than 87% of patients were of Caucasian ethnicity. African-Americans comprised the second most prevalent ethnicity (8.9%), with a small number of Latinos (1.4%) and patients of other ethnicities (1.9%). There were no significant differences among ethnic groups in the distribution of T1 vs T2 disease ($p = 0.25$).

The relationship of clinical stage with pathological outcome (EPE, positive surgical margins and SVI) is summarized in table 2. Patients with cT2b or cT2c lesions had an increased risk of EPE and SVI compared to cT1c. In contrast, patients with cT2a disease were not at increased risk for these pathological outcomes compared to cT1c. Clinical

Table 1. *Patient demographic data*

	No. Pts (%)	Mean Pt Age	No. Caucasian (%)	No. African-American (%)	No. Latino (%)	No. Other (%)
cT1	2,542 (52)	61	2,219 (52)	244 (56)	32 (46)	47 (51)
cT2a	1,112 (23)	61	1,001 (23)	69 (16)	23 (33)	19 (20)
cT2b	360 (7)	62	317 (7)	32 (7)	5 (7)	6 (7)
cT2c	885 (18)	62	765 (18)	90 (21)	9 (13)	21 (23)
Totals	4,899 (100)		4,302 (88)	435 (9)	69 (1)	93 (2)

stage was not associated with positive surgical margins.

Pretreatment PSA, biopsy Gleason score and PPB were more strongly associated with pathological outcome than was clinical stage (table 2). Patients in each increasing PSA risk group and those with higher PPB were at increased risk of all pathological outcomes studied. Results were similar when PSA was included as a continuous or log-transformed variable (data not shown). Biopsy Gleason score was strongly associated with EPE and SVI but not with positive margin status.

During a mean and median followup of 42.5 ± 30.5 and 35.8 months, respectively, 741 patients (15.3% of study cohort) had biochemical recurrence. The associations of clinical stage, PSA, PPB and biopsy Gleason score with biochemical recurrence after radical prostatectomy are summarized in table 3. Using cT1c as a reference, cT2b was associated with recurrence on univariate analysis. However, this finding did not hold true in the multivariable model controlling for the other clinical parameters studied (PSA, PPB, biopsy Gleason score). On multivariable analysis clinical stage was not associated with the risk of biochemical recurrence after radical prostatectomy. Compared to cT1c, none of the higher clinical stage groups were at increased risk for biochemical recurrence. A similar result was obtained in a multivariable model comparing all cT1 to all cT2 tumors, when subclassifications within T-stage were removed (HR 1.01 for cT2 relative to cT1 tumors, $p = 0.85$). In contrast, pretreatment PSA, PPB and biopsy Gleason score were all strongly associated with biochemical recurrence, with the risk of recurrence increasing consistently with increasing levels for each variable (table 3). Similar findings were obtained in a separate analysis from which patients receiving adjuvant androgen deprivation therapy or radiotherapy were not excluded (data not shown).

For the full model including clinical stage the AIC was 8,624.1. For the model including all variables except stage, the AIC was virtually identical

Table 2. *Association of clinical variables with pathological outcome after radical prostatectomy (logistic regression analysis)*

	Odds Ratio (95% CI)		
	EPE	Pos Surgical Margins	SVI
Clinical stage:			
cT1c	Reference	Reference	Reference
cT2a	1.09 (0.89–1.33)	0.89 (0.74–1.08)	1.11 (0.78–1.57)
cT2b	1.55 (1.17–2.06)*	1.16 (0.88–1.53)	1.97 (1.31–2.96)*
cT2c	1.37 (1.12–1.68)*	1.05 (0.86–1.27)	1.62 (1.17–2.23)*
PSA (ng/ml):			
0–10	Reference	Reference	Reference
11–20	1.63 (1.32–2.02)*	1.39 (1.13–1.71)*	2.70 (2.01–3.60)*
21–30	1.79 (1.12–2.84)*	1.75 (1.12–2.74)*	1.59 (0.80–3.10)
Greater than 30	4.36 (2.29–8.31)*	2.52 (1.45–4.39)*	4.49 (2.41–8.39)*
PPB:			
0–10	Reference	Reference	Reference
11–33	1.52 (1.11–2.09)*	1.33 (1.03–1.72)*	1.17 (0.68–2.01)
34–50	2.11 (1.52–2.94)*	1.69 (1.28–2.22)*	1.56 (0.89–2.72)
51–75	2.50 (1.71–3.66)*	2.24 (1.62–3.11)*	1.92 (1.03–3.56)*
Greater than 75	2.59 (1.73–3.89)*	2.13 (1.49–3.03)*	2.46 (1.30–4.65)*
Gleason score:			
3+3	Reference	Reference	Reference
3+4	1.37 (1.12–1.68)*	1.17 (0.97–1.41)	1.65 (1.21–2.25)*
4+3	1.82 (1.36–2.43)*	1.01 (0.76–1.34)	2.92 (1.98–4.31)*
4+4 or Greater	2.43 (1.76–3.43)*	1.31 (0.94–1.81)	2.37 (1.49–3.78)*

* Statistically significant.

Table 3. *Association of clinical variables with biochemical recurrence after radical prostatectomy (Cox multivariable regression analysis)*

	Hazard Ratio (95% CI)	p Value
Clinical stage:		
cT1c	Reference	Reference
cT2a	1.05 (0.84–1.32)	0.66
cT2b	1.24 (0.95–1.62)	0.11
cT2c	0.90 (0.72–1.13)	0.36
PSA (ng/ml):		
0–10	Reference	Reference
11–20	2.39 (1.97–2.90)*	<0.01
21–30	3.26 (2.35–4.53)*	<0.01
Greater than 30	5.42 (3.81–7.71)*	<0.01
PPB:		
0–10	Reference	Reference
11–33	0.92 (0.64–1.34)	0.67
34–50	1.31 (0.90–1.91)	0.15
51–75	1.66 (1.10–2.51)*	0.02
Greater than 75	1.76 (1.15–2.70)*	0.01
Gleason score:		
3+3	Reference	Reference
3+4	1.28 (1.03–1.59)*	0.02
4+3	2.04 (1.55–2.70)*	<0.01
4+4 or Greater	3.18 (2.43–4.16)*	<0.01

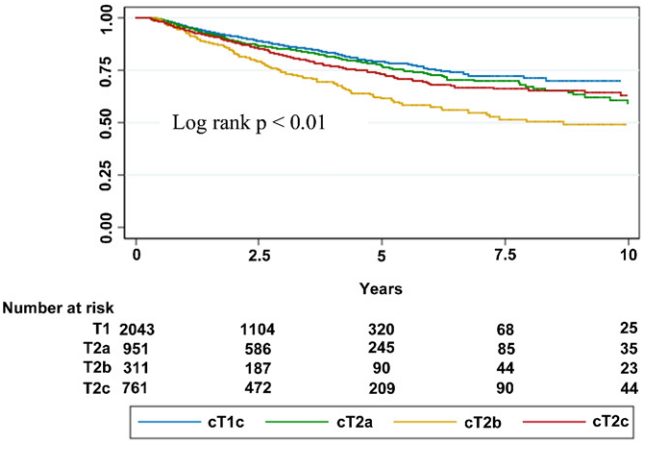
* Statistically significant.

at 8,624.8. The likelihood ratio test did not show a statistically significant difference between the 2 models ($p = 0.15$). A Kaplan-Meier plot illustrating biochemical recurrence-free survival according to clinical stage is shown in the figure. Although univariate analysis revealed worse outcomes for cT2b lesions (log rank $p < 0.01$), this difference was nonsignificant on multivariable analysis.

DISCUSSION

Clinical staging criteria for prostate cancer use DRE and imaging findings to predict the true pathological stage of disease. Pathological stage is closely correlated with the risk of biochemical recurrence after radical prostatectomy.[11] Advanced clinical stage is presumed to predict for adverse pathology and, thus, should identify those patients at increased risk for biochemical recurrence after definitive surgery. However, the failure of clinical stage to accurately predict pathological stage has been well documented in previous studies.[12] This study further questions the usefulness of clinical stage, finding that increasing substage among localized tumors was not associated with biochemical recurrence.

In a multivariable model controlling for other widely used clinical variables (pretreatment PSA, biopsy Gleason score, PPB) clinical stage T2 vs T1 was not associated with an increased risk of biochemical recurrence after radical prostatectomy. In contrast, the other clinical variables studied such as PSA, biopsy Gleason score and PPB were all strongly associated with recurrence. Additionally, clinical stage was only moderately associated with adverse pathological end points. However, the other clinical variables studied were strongly related to these surrogate outcomes.



Kaplan-Meier plot illustrating biochemical recurrence-free survival after radical prostatectomy by clinical stage.

The published literature has frequently questioned the usefulness of staging criteria in predicting prostate cancer outcomes. Two recent studies reported no difference in biochemical recurrence rates between subclassifications of pathological stage T2 tumors.[13,14] Additionally, prior studies investigating differences in outcomes after radical prostatectomy for clinical T1 vs T2 disease have reached conflicting results.[15–18] Armatys[15] and Billis[16] et al compared cT1 vs cT2 tumors, and reported differences in final pathological stage but no differences in biochemical recurrence rates. However, these studies were likely underpowered to detect a true difference in recurrence rates, with sample sizes of less than 300 patients and median followup periods of only 14 and 16 months. Ramos et al reported on a larger series of 1,620 patients in whom radical prostatectomy was performed by a single surgeon.[18] On multivariable analysis the risk of cancer recurrence was decreased for cT1c vs cT2a and T2b disease. Similarly Ghavamian et al reported differences in recurrence rates by clinical stage.[17] However, this difference only reached statistical significance when comparing cT1c to cT2b/cT2c lesions because cT2a was not associated with an increased risk of recurrence. To our knowledge our study is the largest published to date investigating the association of clinical stage with biochemical recurrence rates for localized disease.

The current clinical staging system is based on criteria that predate widespread adoption of PSA screening for prostate cancer and subsequent updates to the system have been relatively minor. Meanwhile PSA screening has produced a significant stage migration toward lower stage, less advanced disease.[8] The majority of today's tumors are detected early, before they become palpable on DRE or visible on TRUS. Therefore, it is possible that abnormalities on DRE in the modern era are more likely to represent benign lesions and not cancer.[19] Prostate cancers detected in these patients are in fact more likely to be incidental tumors, in a separate region of the gland and distinct from the palpable nodule. Thus, these tumors would behave no differently than cT1c lesions despite a classification as cT2, resulting in similar recurrence rates after radical prostatectomy.

Furthermore, the finding of a palpable nodule on DRE is assumed to indicate a larger volume tumor, which presumably portends a worse prognosis. However, PPB also serves as a surrogate measure of tumor volume. In fact, with extended pattern biopsy schemes PPB may be a more accurate marker of tumor volume than DRE findings. In recent years several multivariable nomograms have incorporated PPB as 1 of their predictive

variables.[3,5] In these modern nomograms as in our analysis incorporation of PPB appears to obviate any independent prognostic information offered by clinical stage.

In addition, determination of clinical stage whether by DRE or TRUS is highly subjective with substantial variation across examining urologists.[20] Although measurement of PSA is subject to some variability by assay[21] and day-to-day variation,[22] and assignment of Gleason score is marked by a degree of interobserver variation among pathologists,[23] these measurements are likely more reproducible than determination of clinical stage and, thus, serve as more objective markers of disease severity.

Particularly noteworthy is the finding that cT2b lesions were associated with worse outcome than the supposedly more advanced cT2c tumors. A number of previously published nomograms for the prediction of pathological and biochemical outcomes have likewise assigned more points toward a prediction of adverse outcome for T2b than T2c tumors.[24–27] Moreover a more recent nomogram reports an increased risk of prostate cancer specific mortality in cases staged cT2a relative to cT1c.[28] These inconsistent findings may be due to common inaccuracies in the application of clinical staging criteria. Specifically a nonpalpable or unilaterally palpable nodule on rectal examination but bilateral disease on biopsy may be incorrectly staged as cT2c. Therefore, these incorrectly staged lesions would behave in a fashion similar to cT2a tumors. On the other hand, the widely used D'Amico risk classification[6] adopted by the American Urological Association's updated 2007 clinical practice guideline for prostate cancer[29] assigns any patient with a cT2c lesion to high risk regardless of PSA or biopsy Gleason score. Our data, by contrast, suggest that clinical stage T2c alone should not be sufficient for classification in this high risk category.[30]

Our study is not without limitations. Our data set is derived from a diverse group of primarily community based urological practices. Certainly variations in physical examination skills, TRUS interpretation, biopsy techniques, pathological review or patient followup among practitioners could potentially skew our data. However, the variation of practice patterns in this data set also serves as a strength of our study as our data should better predict outcomes for the average patient seen in the community compared to those seen by a single practitioner in a high volume academic setting. Additionally, our cohort was limited to patients who underwent radical prostatectomy and those patients treated with primary radiation therapy were excluded from study. As patients selected for surgery may have a more favorable risk profile our conclusions regarding the lack of usefulness of clinical stage may not be generalizable to those undergoing primary radiation therapy. Finally the analyses were not corrected for multiple comparisons. However, none of the conclusions hinge on findings of marginal statistical significance and so statistical error is unlikely to explain the findings.

CONCLUSIONS

Compared to clinical stage, the other clinical variables analyzed in our study (pretreatment PSA, biopsy Gleason score, PPB) were more strongly associated with pathological outcome and biochemical recurrence after radical prostatectomy. None of these variables alone is a perfect prognostic instrument. However, when used in combination these clinical indicators are strongly predictive of patient outcome. These variables and not clinical stage should be emphasized in counseling men with prostate cancer who plan to undergo radical prostatectomy, and in developing future multivariable prognostic instruments and risk stratification systems.

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