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Original Article

Inaccuracies in Assignment of Clinical Stage for Localized Prostate Cancer

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BACKGROUND: Recent data have suggested that clinical T stage is not independently associated with biochemical recurrence of localized prostate cancer after radical prostatectomy. One explanation for this lack of predictive power may be the inaccurate application of staging criteria. **METHODS:** Data from men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database with localized prostate cancer (clinical T1-T2) were analyzed. Correct stage was determined by digital rectal examination (DRE) and transrectal ultrasound (TRUS) findings and was compared with the clinical stage reported directly by the practitioner. DRE/TRUS findings and biopsy results were evaluated to determine factors influencing staging errors. The ability of corrected stage to predict biochemical disease recurrence after prostatectomy was assessed using multivariable analysis. **RESULTS:** Clinical stage was assigned incorrectly in 1370 of 3875 men (35.4%). Errors more commonly resulted in patient downstaging than upstaging (55.1% vs 44.9%; $P < .001$). Patients with TRUS lesions were more likely to be staged incorrectly than those with abnormal DRE findings (65.8% vs 38.2%; $P < .001$). Biopsy laterality was found to strongly influence stage assignment. Even after correction of staging errors, there was no association noted between clinical stage and biochemical disease recurrence after radical prostatectomy. **CONCLUSIONS:** Errors in applying clinical staging criteria for localized prostate cancer are common. TRUS findings are frequently disregarded, and practitioners incorrectly incorporate biopsy results when assigning stage. However, staging errors do not appear to account for the inconsistent reliability of clinical stage in predicting prostate cancer outcomes. These findings further challenge the utility of a DRE-based and/or TRUS-based staging system for risk assessment of localized prostate cancer. *Cancer* **2011;117:283–9.** © *2010 American Cancer Society.*

KEYWORDS: prostatic neoplasms, neoplasm staging, diagnostic errors, digital rectal examination, ultrasonography.

Beginning in 1991, the American College of Surgeons Commission on Cancer required routine cancer staging for all nonpediatric tumors for which staging criteria had been developed.[1] According to the American Joint Committee on Cancer (AJCC), these staging criteria are designed to serve several purposes: helping to predict a patient's prognosis, assisting in the planning of treatment strategies, and providing a common language for practitioners to report the extent of disease.[2,3]

As such, the clinical staging system for localized prostate cancer (clinical T1-T2 disease) is commonly used by today's practitioners in assessing prostate cancer prognosis.[4] Furthermore, clinical stage is included as a component of several frequently cited multivariable prognostic instruments.[5,6] However, recent evidence suggests that this staging system is of limited utility in predicting prostate cancer outcomes,[7] thus abrogating a primary goal of cancer staging. In contemporary multivariable models incorporating powerful predictors such as prostate-specific antigen (PSA), Gleason score, and percentage of positive biopsy cores, it appears that clinical staging criteria offer limited, if any, independent prognostic information in predicting recurrence of localized prostate cancer among radical prostatectomy patients.[7-10]

There are several possible explanations as to why clinical stage does not appear to predict for biochemical disease recurrence after radical prostatectomy.[7] The inclusion of more strongly predictive variables such as percentage of positive biopsy cores in multivariable models may negate any independent prognostic power offered by clinical stage. Alternatively, current clinical staging techniques may lack the sensitivity to reliably determine tumor extent. Lastly, confusion regarding correct interpretation and application of clinical staging criteria may lead to errors in clinical stage assignment

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and diminish the predictive power of clinical stage. These staging errors could potentially defeat another main goal of cancer staging: providing a common language for reporting disease extent.

Although preliminary evidence points to confusion in the urologic community regarding the correct application of clinical staging criteria,[11,12] to the best of our knowledge, the true extent of staging errors in the United States is unknown. We therefore aimed to characterize the prevalence of clinical stage misassignment in a multi-institutional national disease registry and to identify factors influencing staging errors. We then performed an analysis to determine whether inaccuracies in clinical stage assignment can explain the lack of prognostic power offered by stage in predicting prostate cancer recurrence after radical prostatectomy.

MATERIALS AND METHODS

We performed an analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, a national disease registry of men with prostate adenocarcinoma recruited from 40 academic-based and community-based urology practices across the United States. The registry assesses 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 is 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 their physicians' usual practice patterns and are followed until death or withdrawal from the study. Details of the database methodology have been published previously.[13,14]

Our analysis included all patients in the CaPSURE database with clinically localized (cT1 and cT2) adenocarcinoma of the prostate who were diagnosed between 1995 and 2008. Participating clinicians directly report digital rectal examination (DRE) and transrectal ultrasound (TRUS) results to CaPSURE, including the presence or absence of a palpable nodule on DRE or visible lesion on TRUS, as well as lesion laterality. The assigned clinical stage was defined as the clinical T stage reported directly to the database managers from the participating CaPSURE clinicians. This assigned clinical stage was based on each practitioner's individual interpretation of the clinical staging criteria.

We then defined corrected clinical stage according to AJCC staging criteria, as follows: cT1 indicated tumor not palpable or visible by imaging, cT2a/cT2b indicated tumor with a unilateral palpable nodule and/or unilateral lesion on imaging, and cT2c indicated tumor with bilaterally palpable nodules and/or bilaterally visible lesions on imaging.[3] Biopsy results were not factored into assignment of corrected clinical stage. Tumors classified as cT2a and cT2b were grouped together because CaPSURE does not include data regarding the fraction of the lobe involved by tumor. Tumors classified as cT2 by practitioners without further discrimination were excluded because this ambiguous classification does not indicate the unilateral versus bilateral nature of the lesion.

The prevalence of staging errors was then determined by comparing the assigned clinical stage with the corrected clinical stage for each patient. Men in whom assigned clinical stage differed from corrected clinical stage were deemed to have been staged incorrectly. The Fisher exact and chi-square tests were used to determine whether the presence or absence of lesions on DRE and TRUS or the laterality of positive biopsy results were associated with clinical stage misassignment.

To determine whether correction of staging errors improved the ability of clinical stage to predict cancer recurrence, multivariable Cox proportional hazards regression analysis was then performed to examine the association between corrected clinical stage and biochemical disease recurrence after radical prostatectomy. This analysis included all patients in the CaPSURE database with clinically localized disease (cT1-cT2) who underwent radical prostatectomy as their primary treatment. Patients treated with neoadjuvant or adjuvant androgen deprivation or radiotherapy were excluded from the analysis. As noted earlier, men classified as having cT2 disease without further discrimination were excluded in the primary model. In a secondary model, these men were included as a separate group.

These regression models were performed using the corrected clinical stage (based on reported DRE and TRUS data); a similar analysis based on assigned (directly reported) stage has been published previously.[7] The model controlled for year of diagnosis, preoperative PSA level, biopsy Gleason score, and percentage of positive biopsy cores when calculating recurrence risk. Biochemical disease recurrence was defined as a PSA >0.2 ng/mL on 2 measurements[15] or any secondary treatment at least 6 months after surgery.

Table 1. Clinician-Assigned Clinical Stage According to DRE and TRUS Findings[a,b]

Finding	T1c No.	T2a/b No.	T2c No.	Total
Normal DRE and TRUS	1353 (91.4%)	74 (5.0%)	53 (3.6%)	1480
Unilateral DRE abnormality	35 (2.6%)	855 (63.3%)	461 (34.1%)	1351
Unilateral TRUS abnormality	346 (47.7%)	262 (36.1%)	118 (16.3%)	726
Unilateral DRE or TRUS abnormality	371 (21.1%)	903 (51.2%)	488 (27.7%)	1762
Bilateral DRE abnormality	1 (<0.1%)	132 (44.7%)	162 (54.9%)	295
Bilateral TRUS abnormality	193 (50.5%)	72 (18.8%)	117 (30.6%)	382
Bilateral DRE or TRUS abnormality	194 (30.6%)	190 (30.0%)	249 (39.3%)	633
Total	1918 (49.5%)	1167 (30.1%)	790 (20.4%)	3875

DRE indicates digital rectal examination; TRUS, transrectal ultrasound.

[a] Frequencies are given with row percentages.

[b] Unshaded regions represent men assigned to the correct clinical classification. Light gray-shaded regions represent men assigned to an inappropriately high clinical classification (upstaged). Dark gray-shaded regions represent men assigned to an inappropriately low clinical classification (downstaged).

RESULTS

Prevalence of Staging Errors

Table 1 shows the clinical stage assigned by CaPSURE practitioners according to DRE/TRUS findings. Staging errors occurred in 1370 of the 3875 men (35.4%) who met the study inclusion criteria. Assignment of an inappropriately low clinical stage (downstaging) accounted for 55.1% of staging errors, whereas assignment of an inappropriately high clinical stage (upstaging) accounted for 44.9%.

Impact of DRE or TRUS Findings on Staging Errors

Staging errors were more common in men with abnormalities on DRE or TRUS compared with those with normal DRE/TRUS findings. Of the men with normal DRE and TRUS results, only 8.6% of 1480 men were staged incorrectly. In contrast, 51.9% of 2395 men with abnormalities on DRE or TRUS were assigned the incorrect clinical stage.

Staging errors were more common in patients with abnormal TRUS findings compared with those with abnormal DRE results. Of 1108 men with lesions noted on TRUS, 65.8% were staged incorrectly. In contrast, only 38.2% of 1646 of men with abnormalities noted on DRE were assigned an incorrect clinical stage.

Of the 755 downstaged patients, 575 (76.2%) were incorrectly assigned to clinical T1c. Table 2 shows the DRE and TRUS findings in these patients. Disregard for TRUS lesions occurred in 93.7% of these men inappropriately assigned to clinical T1c. In contrast, only 6.3% of these patients were noted to have abnormalities on DRE.

Table 2. DRE and TRUS Findings in Patients Incorrectly Assigned to Clinical Stage cT1c

Finding	DRE Nodule No.	TRUS Lesion No.	Total
Unilateral lesion	35	346	381 (66.3%)
Bilateral lesion	1	193	194 (33.7%)
Total	36 (6.3%)	539 (93.7%)	575

DRE indicates digital rectal examination; TRUS, transrectal ultrasound.

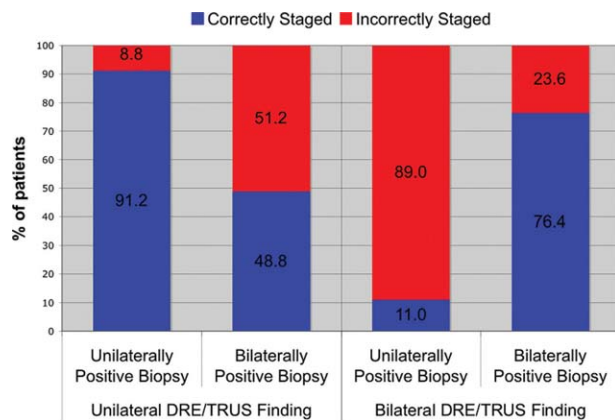### Impact of Biopsy Laterality on Staging Errors

The remainder of staging errors occurred when men were inappropriately assigned to clinical stage T2a, T2b, or T2c. These errors accounted for 23.8% of downstaged patients and all upstaged patients. Information regarding the laterality of positive biopsy results was available for 88.3% of these 1805 men. The impact of biopsy laterality on staging errors in these patients is shown in Table 3.

The likelihood of staging errors was significantly modified by biopsy laterality. Of the 217 men incorrectly assigned to clinical stage T2a/b, 191 (88.0%) had unilaterally positive biopsies, whereas biopsies were bilaterally positive in only 26 men (12.0%). Conversely, of the 494 men incorrectly assigned to clinical stage T2c, biopsy results were unilaterally positive in only 79 (16%), compared with 415 men (84.0%) in whom biopsy results were bilaterally positive.

Figure 1 shows the prevalence of staging errors according to both DRE/TRUS results and biopsy laterality. AJCC staging criteria state that all patients with unilateral DRE/TRUS abnormalities should be assigned to clinical stage T2a/b. Of all men with unilateral DRE/TRUS lesions and unilaterally positive biopsy results, 91.2% were correctly assigned to this clinical stage.

Table 3. Biopsy Laterality in Patients Incorrectly Assigned to Clinical cT2a/b and cT2c Stage

	Men Incorrectly Assigned cT2a/b No.	Men Incorrectly Assigned cT2c No.	Total
Unilaterally positive biopsy	191 (88.0%)	79 (16.0%)	270 (38.0%)
Bilaterally positive biopsy	26 (12.0%)	415 (84.0%)	441 (62.0%)
Total	217 (30.5%)	494 (69.5%)	711

Table 4. Distribution of Assigned and Corrected Clinical Stage

Clinical Stage	Assigned by Clinician No.	Corrected According to DRE/TRUS Findings No.
T1c	1918 (49.5%)	1480 (38.2%)
T2a/b	1167 (30.1%)	1762 (45.5%)
T2c	790 (20.4%)	633 (13.3%)

DRE indicates digital rectal examination; TRUS, transrectal ultrasound.

Figure 1. Staging errors according to digital rectal examination (DRE)/transrectal ultrasound (TRUS) findings and biopsy laterality are shown.

However, of those men with unilateral DRE/TRUS lesions but bilaterally positive biopsies, only 48.8% were assigned to the correct clinical stage (cT2a/b) and 51.2% were incorrectly assigned to clinical T2c. Conversely, the correct clinical stage for all men with bilateral DRE/TRUS lesions is cT2c. In men with these bilateral lesions and bilaterally positive biopsy results, 76.4% were correctly assigned to clinical stage T2c. However, of men with bilateral DRE/TRUS lesions but unilateral positive biopsy results, only 11.0% were correctly classified as having cT2c disease, whereas 89.0% were incorrectly classified as having clinical T2a/b disease.

Biopsy laterality was found to be a stronger predictor of assigned clinical stage than DRE/TRUS findings. The likelihood of being staged with cT2a/b disease was found to be 2.5 times higher (95% confidence interval [95% CI], 2.0-3.1) in patients with unilaterally positive biopsies than in patients with unilateral DRE/TRUS findings. Similarly, patients with bilaterally positive biopsies were 1.2 times more likely (95% CI, 1.1-1.3) to be staged as

having cT2c disease compared with patients with bilateral DRE/TRUS findings.

Correction of Staging Errors: Impact on Predictive Power of Clinical Stage

The distribution of assigned clinical stage compared with corrected clinical stage is shown in Table 4. Correction of staging errors increased the percentage of patients staged as having cT2a/b disease from 30.1% to 45.5%, and decreased the percentage of patients staged as having cT1c and cT2c disease.

The results of the multivariable Cox proportional hazards regression model summarizing the associations of corrected clinical stage, PSA level, biopsy Gleason score, and percentage of positive biopsy cores with biochemical disease recurrence after radical prostatectomy are summarized in Table 5. The model used corrected clinical stage based on directly reported DRE and TRUS findings. No association was observed between advanced clinical T2 stage and risk of biochemical disease recurrence. In contrast, a strong association was identified between increasing PSA level, advanced biopsy Gleason score, and percentage of positive biopsies >33% and the risk of disease recurrence. Similar results were obtained in a secondary model in which patients assigned clinical T2 stage (without further designation) were included as a separate group (data not shown).

DISCUSSION

The current study reports a high prevalence of stage misassignment in a multi-institutional, community-based prostate cancer registry. Based on AJCC staging criteria for localized prostate cancer,[3] 35.4% of the patients in our cohort were staged incorrectly. The majority of these staging errors appear to be due to disregard for TRUS findings and inappropriate consideration of biopsy results when assigning clinical stage.

Table 5. Association of Clinical Variables With Biochemical Disease Recurrence After Radical Prostatectomy in Model Using Corrected Clinical Stage (Cox Multivariable Regression Analysis)

Variable		Corrected Clinical Stage	
		HR (95% CI)	*P*
Clinical stage	cT1c	Reference	Reference
	cT2a/b	1.14 (0.95-1.37)	.15
	cT2c	1.08 (0.86-1.36)	.51
PSA, ng/mL	0-10	Reference	Reference
	11-20	2.35 (1.95-2.84)	<.01
	21-30	2.97 (2.12-4.17)	<.01
	>30	4.30 (3.11-5.96)	<.01
Gleason score	3 + 3	Reference	Reference
	3 + 4	1.26 (1.02-1.56)	.03
	4 + 3	1.98 (1.53-2.57)	<.01
	≥4 + 4	3.37 (2.67-4.26)	<.01
% Positive biopsy cores	0-10	Reference	Reference
	11-33	1.00 (0.72-1.38)	.98
	34-50	1.40 (1.01-1.94)	.04
	51-75	1.77 (1.24-2.52)	<.01
	>75	1.68 (1.17-2.43)	<.01

HR indicates hazard ratio; 95% CI, 95% confidence interval; PSA, prostate-specific antigen.

These results build on the findings of several small series that have previously reported significant variations in the interpretation and application of clinical staging criteria. Campbell et al reported a study of 12 sample prostate cancer cases staged by 20 physicians with expertise in prostate cancer and found that the overall agreement for the assignment of T stage was only 63.9%.[11] This finding was further illustrated by Sexton et al, who performed a quality assurance audit on 97 prostate cancer cases in an oncology database and found a 52% discrepancy rate in the assignment of T stage.[12] To our knowledge, the current study is the largest series analyzing errors in prostate cancer stage assignment reported to date, and the first to assess staging errors in a nonexperimental, multi-institutional setting.

In the current study cohort, staging errors more often resulted in downstaging compared with upstaging (55.1% vs 44.9%). These downstaging errors most commonly occurred when imaging findings were ignored and men with lesions noted on TRUS were inappropriately assigned to clinical T1c stage. In fact, abnormalities on TRUS were disregarded in 65.8% of patients in the current study cohort. Although TRUS appears to have utility in predicting outcome in the hands of a single, high-volume practitioner,[16] others have raised questions regarding its interobserver reproducibility, sensitivity and specificity, and utility in defining tumor size and disease extent.[3]

Nonetheless, the most recent version of the AJCC staging manual considers a TRUS lesion sufficient for elevation to clinical T2 stage.[3] Perhaps due to the inconsistently reported utility of TRUS results, we found that the majority of TRUS findings were ignored by CaPSURE practitioners when assigning clinical stage.

It is generally accepted that biopsy results should not be incorporated into clinical stage assignment. Nonetheless, the data from the current study found biopsy laterality to be strongly associated with assignment of clinical stage. Whereas biopsy results were unilaterally positive in 88.0% of patients who were misstaged as cT2a/b, unilateral biopsy results were present in only 16.0% of patients misstaged as cT2c. Conversely, 84.0% of patients misstaged as cT2c had bilaterally positive biopsies, compared with only 12.0% of patients misstaged as cT2a/b with bilaterally positive biopsies. In fact, biopsy laterality was found to be a stronger predictor of stage assignment than DRE or TRUS findings. Men with unilaterally positive biopsies were 2.5 times more likely to be assigned to clinical T2a/b disease than those with unilateral DRE/TRUS findings. Similarly, patients with bilaterally positive biopsies were 1.2 times more likely to be classified as having cT2c disease compared with patients with bilateral DRE/TRUS findings.

The wide variation regarding the role of biopsy results in clinical staging could be attributed to the ambiguous wording of the AJCC staging manual, which states that all of the information that is available before the first definitive treatment may be used for clinical staging.[3] It is our interpretation, however, that biopsy information does not factor into clinical stage assignment; otherwise, by definition, no patient would be assigned to clinical T1c stage. Certainly, clarification regarding the use of biopsy information in stage assignment should result in the more uniform interpretation and application of staging criteria.

Although a clinical stage of cT3 or greater (extraprostatic disease) has been shown to portend an adverse prognosis,[10,17] these lesions are relatively rare, accounting for <5% of all tumors in contemporary series.[18] The vast majority of today's patients present with localized disease, and in these men, there is little evidence to suggest that clinical stage aids in the assessment of prognosis. We have previously shown that clinical stage offered no independent prognostic information when predicting biochemical disease recurrence in patients with organ-confined prostate cancer after controlling for other clinical variables (PSA level, biopsy Gleason score, and percentage of positive biopsy cores).[7] Others have similarly found

no association between clinical stage and rates of disease recurrence after radical prostatectomy, although adverse pathologic findings were found to be more common in cT2 compared with cT1 tumors.[8,9]

Given the ambiguities in the interpretation of clinical staging guidelines, it is possible that the poor prognostic ability of staging is because of the inaccurate application of staging criteria, and resultant stage misassignment. However, the results of the current study indicate that stage misassignment does not explain the poor predictive ability of clinical stage. Our multivariate Cox regression model using corrected clinical stage did not identify an association between advanced clinical stage and risk of biochemical disease recurrence. In contrast, the other clinical variables analyzed (pretreatment PSA level, biopsy Gleason score, and percentage of positive biopsy cores) were all found to correlate strongly with disease recurrence. Thus, correction of staging inaccuracies did not improve the predictive ability of clinical staging criteria.

These findings, coupled with those of prior reports, question the utility of a DRE-based/TRUS-based staging system for prostate cancer, specifically the relevance of the T1 versus T2 designation. The AJCC staging manual readily acknowledges the lack of reproducibility and poor sensitivity and specificity of the imaging modalities used to assess prostate tumors.[3] Significant interobserver variability among DRE findings has been reported as well.[19] Furthermore, the results of the current study demonstrated a widely disparate interpretation of staging guidelines, leading to marked heterogeneity within clinical T stage groups. Finally, clinical disease stage is not independently associated with disease recurrence after radical prostatectomy, even after our attempt to decrease the heterogeneity within staging groups through the uniform application of DRE and TRUS findings when assigning clinical stage.

Despite these shortcomings, clinicians may gain important information from DRE and/or TRUS among patients with localized prostate cancers. Although these tests fail to address 2 of the primary goals of cancer staging, namely to aid in the assessment of prognosis and to provide a common language to facilitate the exchange of information between treatment centers, they may assist the practitioner in the planning of treatment strategies. Some have suggested that a higher clinical stage is associated with an increased risk of positive surgical margins, a finding that may alter the surgeon's decision regarding nerve sparing at the time of radical prostatectomy.[20]

Indeed, the pioneers of the anatomic radical retropubic prostatectomy reported that men with palpable apical lesions are more likely to require excision of the neurovascular bundle, although they argued that final decisions regarding nerve sparing should be based on intraoperative findings, not preoperative data.[21]

The current study is not without limitations. The data set is derived from a diverse group of primarily community-based practices. Variations in physical examination skills and TRUS interpretation certainly could diminish the power of staging. However, the diversity of the participating clinicians also serves as a strength of this study because it better characterizes the range of staging interpretations and applications observed in the community compared with a single practitioner in a high-volume academic setting. Furthermore, we cannot ensure that the same practitioner performed the DRE and TRUS, interpreted the biopsy results, and assigned the clinical stage in all cases. Certainly, the likelihood of staging errors would be increased if any of these data were not available to the clinician responsible for assigning clinical stage.

In addition, CaPSURE data only reflect whether a nodule on DRE or a hypoechoic lesion noted on TRUS is unilateral versus bilateral, but not whether it involves more or less than half of a lobe. Thus, for our analyses, we were forced to combine cT2a and cT2b patients into 1 group. However, because no association with disease recurrence was observed with the supposedly more advanced cT2c lesions, it is unlikely that separation of cT2a and cT2b lesions would reveal different results. The disease recurrence analysis included only patients who underwent radical prostatectomy as definitive treatment. Therefore, our conclusion regarding the lack of utility of clinical stage in predicting biochemical disease recurrence may not be generalizable to patients treated with primary radiotherapy or other treatment modalities, Lastly, further refinements in imaging could better characterize intraprostatic tumor extent and/or better detect those patients with cT3 disease, in whom the risk of disease recurrence is increased.[10,17] These refinements may in turn make clinical T stage a more important predictor of outcome.

The results of the current study indicate that there is wide variation in the interpretation and application of clinical staging criteria. Based on the current AJCC cancer staging guidelines, >35% of patients in our multi-institutional community-based sample were staged incorrectly. Confusion regarding the role of TRUS findings and biopsy results are largely responsible for inaccuracies in stage

assignment. However, staging errors do not appear to be responsible for the failure of clinical stage to predict biochemical disease recurrence in men with localized prostate cancer. These findings argue against the utility of a DRE-based and/or TRUS-based staging system for localized prostate cancer.

CONFLICT OF INTEREST DISCLOSURES

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