Percent Tumor Involvement and Risk of Biochemical Progression After Radical Prostatectomy

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Purpose: Percent tumor involvement has been associated with biochemical progression in organ confined disease, although its role in predicting outcome in men with more advanced disease pathology is unclear. We hypothesized percent tumor involvement may be a good correlate of outcome in all stages of prostate cancer.

Materials and Methods: We examined the association between percent tumor involvement in the radical prostatectomy specimen and the outcome measures of pathological stage and biochemical progression using multivariate logistic regression and Cox proportional hazards analysis, respectively, in 2,220 patients from the Duke Prostate Center radical prostatectomy database.

Results: On multivariate analysis, percent tumor involvement significantly predicted the risk of positive margins ($p < 0.001$), extracapsular extension ($p < 0.001$), seminal vesicle invasion ($p < 0.001$) and biochemical progression (HR 1.16, 95% CI 1.01–1.33, $p = 0.035$). The percent tumor involvement cut points of 5% or less, 6% to 20%, 21% to 50% and greater than 50% significantly separated men in groups with differing biochemical progression risk ($p < 0.001$). In addition, these cut points were further able to stratify men among those with organ confined margin negative disease ($p < 0.001$), either positive margins or extracapsular extension ($p < 0.001$), and those with seminal vesicle invasion ($p = 0.02$).

Conclusions: Percent tumor involvement was a significant predictor of biochemical progression and was able to further stratify men who were already assigned to narrowly defined pathological groups. If confirmed in other studies, percent tumor involvement may enable the clinician to identify the high risk patient who stands to benefit the most from adjuvant therapy.

Key Words: prostatic neoplasms, prostatectomy, recurrence, disease progression

Tumor size is a well established prognostic factor in many types of cancer. Its importance is recognized in kidney cancer staging with tumors less than or equal to 4 cm denoted T_1 and those greater than 4 cm as T_2 lesions.[1] Likewise, percent tumor involvement (tumor size as a percentage of prostate size) is also reflected in the current form of TNM staging for prostate cancer. Specifically tumors less than half of 1 lobe are T_{2a} while those greater than half of 1 lobe are T_{2b}.[2] An alternative measure to percent tumor involvement is tumor volume, which has been found in multiples studies to hold prognostic value in prostate cancer.[3,4] However, other studies have found contradictory results.[5] One major problem with measuring true tumor volume is that it requires specialized procedures such as whole mounting and computerized digitization that are time-consuming and require additional equipment and, therefore, it is not routinely reported by pathologists, at least at our institution. On the contrary, percent tumor involvement is reported at our institution, and is relatively easily provided. This measure simply requires pathologists to visually accrue the percentage of each slide examined that contains tumor and provide an average. This generally adds a minimal amount of review time to each case. Furthermore, percent tumor involvement has been demonstrated to be associated with biochemical progression in organ confined disease,[6,7] although its role in predicting outcome among men with more advanced disease pathology has not been well studied. We hypothesized that percent tumor involvement may be a good correlate of outcome in all stages of prostate cancer.

MATERIALS AND METHODS

Patient Population

After obtaining institutional review board approval, data from patients treated with radical prostatectomy between 1990 and 2006 were abstracted into the Duke Prostate Center database. Of the 4,581 men in the Duke Prostate Center radical prostatectomy database we excluded patients who had received preoperative hormones, chemotherapy or radiation. Patients with missing data for serum PSA, margin status, capsular extension and percent tumor involvement were excluded from analysis. This resulted in a study population of 2,220 patients.

The prostatectomy specimens were harvested in the operating room, left and right sides inked with different colors, weighed, and fixed in formaldehyde overnight at 4C. The apex and the bladder neck margin were shaved and radially

Submitted for publication December 13, 2007.

Supported by the Department of Veteran's Affairs, Department of Defense and the American Urological Association Foundation/Astellas Rising Star in Urology Award.

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sectioned to permit evaluation of the margin status parallel to the urethra. The remaining prostate was then sectioned perpendicular to the rectal surface at 3 to 4 mm intervals and submitted entirely for microscopic evaluation. The tumor involvement of each slide was estimated by the percent of the slide consumed with tumor. Estimation of percent tumor involvement for the entire prostate was accomplished by summing each individual slide and then averaging the results from all slides analyzed.

Biochemical progression was defined as any increase in PSA greater than the 0.2 ng/ml taken after the initial 1 month postoperative period. Patients who underwent adjuvant radiotherapy within 6 months after surgery for an undetectable PSA were excluded from analysis. Among men who did not have biochemical recurrence, mean and median followup was 5.5 (standard deviation 3.7) and 3.8 years (range 0 to 15.7), respectively. During that time 571 (25.7%) men had recurrence.

Statistical Analysis

The distribution and association of percent tumor involvement with other clinicopathological variables was evaluated using the Mann-Whitney U or Kruskal-Wallis test when appropriate. PSA, percent tumor involvement and prostate weight, after log transformation, were analyzed as continuous variables. Race (black or nonblack), clinical stage (cT_1, cT_2 or $cT_{3/4}$), pathological Gleason sum (less than 7, 7 and greater than 7), surgical margins (positive or negative) extracapsular extension (positive or negative) and seminal vesicle invasion (positive or negative) were all examined as categorical variables.

The significant independent risk factors for the binary pathological end points of positive surgical margins, extracapsular extension and seminal vesicle invasion were determined using a multivariate backwards stepwise logistic regression model. The variables considered for entry into the model were percent tumor involvement, preoperative PSA, age, race, clinical stage, pathological Gleason sum, margin status, seminal vesicle involvement, prostate weight and year of surgery. The variable with the highest p value was successively eliminated until only variables with a $p < 0.1$ were included. Similar analyses were performed to determine the independent risk factors for biochemical progression using a Cox proportional hazards analysis.

To determine the independent ability of the percent tumor involvement cut points to predict biochemical progression, we used log rank tests and a Cox proportional hazards model mutually adjusting for year of surgery, PSA, race, clinical stage, pathological Gleason sum, positive surgical margins, extracapsular extension and seminal vesicle invasion. We tested for trend by entering the median percent tumor involvement of each percent tumor volume group as a continuous term into the model and evaluated the coefficient by the Wald test. A total of 15 men had lymph node positive disease. When these men were included or excluded from analysis, the results did not materially change. Therefore, these patients were included and assigned the disease pathology group corresponding to the findings from the primary prostatectomy specimen. All statistical analyses were performed using SPSS® 12.0 and STATA® 9.0.

RESULTS

Demographics

The majority of patients were white, had clinical stage T_1 disease, had PSA less than 10 ng/ml and had organ confined disease on final pathological analysis (table 1).

Predictors of Adverse Pathology

To determine the significant independent predictors of adverse pathological findings after radical prostatectomy we used multivariate analysis and found that percent tumor involvement significantly predicted the risk of positive surgical margins ($p < 0.001$), extracapsular extension ($p < 0.001$) and seminal vesicle invasion ($p < 0.001$) (table 2). The only other factors which significantly predicted all 3 adverse pathological features studied were PSA and pathological Gleason sum.

Predictors of Biochemical Progression

On multivariate analysis percent tumor involvement was a significant predictor of biochemical progression (HR 1.16, 95% CI 1.01–1.33, $p = 0.035$, table 3). In addition, the known prognostic factors of PSA, clinical stage, pathological grade and findings along with prostate weight were also significantly associated with progression.

Determination of PTI Cut Points

Given that percent tumor involvement significantly predicted all 3 pathological end points as well as progression,

TABLE 1. *General demographics of men treated with radical prostatectomy in the Duke Prostate Center database*

No. race (%):		
Black	330	(15.0)
Nonblack	1,885	(85.0)
Age:		
Mean (SD)	62.6	(7.43)
Median (IQR)	63.0	(57.6–68.1)
No. younger than 60 (%)	790	(35.6)
No. 60–69 (%)	1,058	(47.7)
No. older than 69 (%)	371	(16.7)
No. clinical stage (%):		
T_1	1,558	(79.4)
T_2	386	(19.7)
T_3/T_4	19	(1.0)
Diagnosis PSA (ng/ml):		
Mean	9.46	(12.9)
Median	6.4	(4.6–9.6)
No. 4 or less (%)	376	(17.0)
No. 4–10 (%)	1,328	(59.8)
No. greater than 10 (%)	516	(23.2)
No. biopsy Gleason (%):		
Less than 7	1,518	(71.5)
7	454	(21.4)
Greater than 7	152	(7.2)
No. pathological Gleason (%):		
Less than 7	1,012	(45.7)
7	958	(43.2)
Greater than 7	246	(11.1)
No. ECE (%):		
Pos	639	(28.8)
Neg	1,581	(71.2)
No. SV invasion (%):		
Pos	196	(8.8)
Neg	2,024	(91.2)
No. biochemical progression (%):		
Pos	571	(25.7)
Neg	1,649	(74.3)
No. PTI (%):		
Less than 5	682	(30.7)
6–20	989	(44.6)
21–50	484	(21.8)
Greater than 50	65	(2.9)