Is a Positive Bladder Neck Margin Truly a T4 Lesion in the Prostate Specific Antigen Era? Results From the SEARCH Database

W. Cooper Buschemeyer, III, Robert J. Hamilton, William J. Aronson, Joseph C. Presti, Jr., Martha K. Terris, Christopher J. Kane, Christopher L. Amling and Stephen J. Freedland*

From the Departments of Surgery (Division of Urologic Surgery) (WCB, RJH, SJF) and Pathology (SJF), Duke University School of Medicine and Urology Section, Surgical Service, Veterans Affairs Medical Center Durham (WCB, SJF), Durham, North Carolina, Department of Surgery (Urology), University of Toronto (RJH), Toronto, Ontario, Canada, Urology Section, Surgical Service, Veterans Affairs Greater Los Angeles Healthcare System and Department of Urology, University of California-Los Angeles School of Medicine, Los Angeles (WJA), Department of Urology, Stanford University School of Medicine and Urology Section, Surgical Service, Veterans Affairs Medical Center Palo Alto, Palo Alto (JCP) and Urology Section, Surgical Service, Veterans Affairs Medical Center San Francisco and Department of Urology, University of California-San Francisco School of Medicine, San Francisco (CJK), California, Urology Section, Veterans Affairs Medical Center and Section of Urology, Medical College of Georgia, Augusta (MKT), Georgia, and Division of Urology, University of Alabama Birmingham (SJF), Birmingham, Alabama

Purpose: Positive bladder neck margins after radical prostatectomy are currently designated as pT4 lesions. However, to our knowledge the prognostic significance of a positive bladder neck margin in the prostate specific antigen era is unknown. We examined the association between positive bladder neck margins and prostate specific antigen recurrence relative to other pathological findings.
Materials and Methods: We examined 1,722 men from the Shared Equal Access Research Cancer Hospital Database who were treated with radical prostatectomy without lymph node metastases. Time to prostate specific antigen recurrence was compared in men with positive vs negative bladder neck margins using Cox proportional hazards models adjusted for multiple clinical and pathological features.
Results: A positive bladder neck margin in 79 patients (5%) was significantly associated with other poor prognostic features, including higher prostate specific antigen, higher pathological Gleason sum, extracapsular extension, seminal vesicle invasion and other positive margins. After adjusting for clinical and pathological characteristics positive bladder neck margins were associated with an increased risk of prostate specific antigen recurrence (HR 1.52, 95% CI 1.06–2.19, $p = 0.02$). Relative to organ confined margin negative disease a positive bladder neck margin associated with other positive margins showed a recurrence risk that was similar to that of seminal vesicle invasion (HR 4.14, 95% CI 2.55–6.73 and HR 4.22, 95% CI 3.08–5.78, respectively, each $p < 0.001$). An isolated positive bladder neck margin was a rare event, noted in 15 patients (0.7%). In these men the recurrence risk was difficult to estimate due to the small number. However, the HR was similar to that in men with nonbladder neck positive margins or extracapsular extension (HR 2.65, 95% CI 0.97–7.25, $p = 0.06$ and HR 2.19, 95% CI 1.71–2.82, $p < 0.001$, respectively).
Conclusions: In the current study a positive bladder neck margin was frequently associated with other adverse features. When it was concomitant with other positive margins, a positive bladder neck margin was associated with a progression risk similar to that of seminal vesicle invasion (T3b disease). Although men with an isolated positive bladder neck margin had a more favorable pathological profile, there were too few of them to assess outcome reliably. However, the limited data suggest that they may best be categorized as having pT3a disease.

Key Words: prostate, prostatic neoplasms, prostatectomy, bladder, neoplasm staging

In the PSA era gross bladder invasion is rarely noted during RP. Today most bladder invasion is detected as a microscopic +BN. While this is currently considered a pT4 lesion,[1] it is unclear whether the prognosis justifies this designation. Indeed, multiple recent studies demonstrated that the risk of biochemical progression associated with a +BN is more consistent with pT3 than with pT4.[2–7] However, whether a +BN shows worse outcomes than positive margins at other locations is debated. Some investigators found that of men with a positive margin those with a +BN had worse outcomes,[2,4] while others found that a +BN portended no greater risk.[3,7,8]

A consistent aspect in these studies is that men with a +BN often had multiple other adverse features, such as high Gleason score, positive margins at other sites, extracapsular extension and SV+. Therefore, the challenge is to delineate the independent predictive value of a +BN. Simply controlling for other pathological features in multivariate models may not accurately depict the relationship between a +BN, other features and biochemical recurrence because all vari-

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* Correspondence and requests for reprints: Division of Urology, Box 2626 Duke University Medical Center, Duke University School of Medicine, Durham, North Carolina 27710 (telephone: 919-668-8361; FAX: 919-668-7093; e-mail: steve.freedland@duke.edu).

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ables are highly related, ie co-linear, which can interfere with multivariate models.[9] Therefore, it is difficult to assess whether the greater recurrence risk noted in some studies was due to the +BN or to associated adverse features.

To properly determine the significance of a +BN we compared the risk of biochemical recurrence between men with a +BN and a –BN on 2 separate analyses. The first analysis compared +BN and –BN, controlling for multiple clinicopathological features. The second compared men in whom a +BN was the only positive margin to men with a +BN in association with other positive margins. To accomplish this we used the multiethnic, multicenter SEARCH database cohort of men treated with RP.[10]

METHODS

Study Population, and Assessment of Clinical and Pathological Variables

After obtaining institutional review board approval to abstract and combine data we entered data on patients treated with RP between 1988 and 2006 at Veterans Affairs Medical Centers in West Los Angeles, Palo Alto and San Francisco, California; Durham, North Carolina; and Augusta, Georgia into the SEARCH database.[10] Patients treated with preoperative androgen deprivation or radiation therapy were excluded. Of the 2,062 patients in the SEARCH database 32 with lymph node metastasis were excluded because they were at high risk for recurrence independent of RP specimen pathology. Additionally, we excluded 308 men with unknown overall margin status and men with known overall positive margin status but in whom the exact anatomical location(s) of the positive margins were unknown. This resulted in a final study population of 1,722 men. Recurrence was defined as a single PSA measurement of greater than 0.2 ng/ml, 2 consecutive values of 0.2 ng/ml or secondary treatment for increased PSA. Men who received adjuvant radiation therapy, defined as radiation within 6 months after surgery for undetectable PSA, were censored as having no recurrence at the time of radiation.

Pathological specimens were sectioned according to the individual protocol at each institution. Briefly, at 3 of the 5 centers step-sectioning was used at 3 to 5 mm intervals and all sections were embedded for analysis. At the fourth center representative sections were used of the apex, base, inferior, mid and superior aspects of the gland, including any grossly evident tumor and seminal vesicles according to the protocol outlined by experienced academic genitourinary pathologists.[11] At the remaining center the distal periurethral plane was removed and sectioned perpendicular to the distal margins, usually in 2 to 4 tissue blocks. The remaining prostate was then sectioned from the distal to the proximal margin, including the SVs. This was submitted in subsequent blocks. If a BN was recognized, it was submitted as a separate block.

Margins were categorized as apex, BN, or left or right peripheral. Information on the number of positive foci at each location (apex, BN, etc) was not available and, thus, cases were defined as positive or negative at each location. The number of positive margins was calculated by adding the number of locations with a positive margin. Each location was considered mutually exclusive. For example, a man with an isolated left apical margin was considered to have a positive apical margin but not a left lateral margin for a total of 1 positive margin.

Statistical Analysis

The distribution of demographic, clinical and pathological variables was compared between men with a +BN vs a −BN using the t test for continuous variables, the chi-square test for categorical variables or the rank sum test for nonnormally distributed continuous variables. For analysis involving categories in which the estimated number of men was less than 5 we used Fisher's exact test. Age, PSA, year of surgery and prostate weight were analyzed as continuous variables, while clinical stage (T1 or T2/T3), race (black, white or other), pathological Gleason score (3 + 3 or less, 3 + 4, or 4 + 3 or greater) and surgical center were analyzed as categorical variables. PSA and prostate weight were examined after logarithmic transformation.

Survival curves were estimated using the Kaplan-Meier technique. Time to biochemical recurrence was compared between men with a +BN or a –BN using Cox proportional hazards models, adjusting for age at surgery, preoperative PSA, race, year of surgery, surgical center, clinical stage, biopsy Gleason score, pathological Gleason score, extracapsular extension, SV+, number of nonBN positive margins and prostate weight. We examined the effect of BMI as a categorical variable (less than 25 kg/m^2, 25 to 29.9, 30 to 34.9 or 35 or greater) on the risk of progression. Its addition to the multivariate model did not affect the HR associated with BN status (data not shown). Therefore, given that BMI data were only available for 80% of patients, it was not included in the final models.

To better categorize +BNs relative to other pathological features we compared time to biochemical recurrence using Cox proportional hazards models in 5 pathological groups, including 1—organ confined, margin negative, 2—T2 with positive margins other than at the BN or T3, ie extracapsular extension, with or without positive margins and SV−, 3—a +BN, other margins negative and SV−, 4—a +BN, other margins positive and SV−, and 5—SV+. Of note, in group 2 men with organ confined and margin positive disease other than a +BN were grouped with men who had extracapsular extension with and without positive margins because these groups have equivalent rates of biochemical recurrence, as previously shown in the SEARCH database.[12]

The distribution of all clinical and pathological variables was similar among the centers and, therefore, data were combined for analysis. All statistical analyses were performed using commercially available software.

RESULTS

Of the 1,722 men in this study a +BN was noted in only 79 (5%). At baseline there were no significant differences in age, year of surgery, BMI or clinical stage between men with a +BN and a −BN (table 1). However, a +BN was significantly associated with other poor prognostic signs, including higher preoperative PSA, higher pathological Gleason sum, extracapsular extension, SV+ and an increasing overall number of positive margins. Of men with a +BN 51% had extracapsular extension, 82% had at least 1 other positive margin and 32% had SV+.

A total of 500 men (30%) experienced biochemical recurrence. Mean ± SD followup in men without biochemical recurrence was 51 ± 42 months (median 40). There were no differences in followup between men with and without a +BN (rank sum $p = 0.80$).