Oncology

Biopsy Perineural Invasion in Prostate Cancer Patients Who Are Candidates for Active Surveillance by Strict and Expanded Criteria

Robert M. Turner II, Todd S. Yecies, Jonathan G. Yabes, Benjamin T. Ristau, Elen Woldemichael, Benjamin J. Davies, Bruce L. Jacobs, and Joel B. Nelson

OBJECTIVE To evaluate the association of biopsy perineural invasion (PNI) with adverse pathologic findings on radical prostatectomy in patients who would have been candidates for active surveillance (AS).

METHODS Using a prospectively populated database of 3084 men who underwent open radical prostatectomy, candidates for AS by strict (Johns Hopkins) and expanded (University of Toronto) criteria were identified. The presence of adverse pathologic features at radical prostatectomy was compared between those men with and without biopsy PNI.

RESULTS Of 596 men who met strict criteria for AS, 16 (3%) had biopsy PNI. In the strict AS cohort, there were no differences in adverse pathologic features at radical prostatectomy between those with and without PNI. Of 1197 men who were candidates for AS by expanded criteria, 102 (9%) had biopsy PNI. Men with biopsy PNI in the expanded AS cohort were more likely to have extraprostatic extension ($P < .001$) and pathologic upgrading ($P = .01$) at prostatectomy. In addition, those with PNI had larger dominant nodules ($P < .001$), and cancer comprised a greater percentage of their prostate glands ($P < .001$). There was no difference in the proportion with a positive margin between the 2 groups ($P = .77$).

CONCLUSION Biopsy PNI was rare in patients who met strict criteria for AS. Among those men who met expanded criteria, PNI was associated with adverse pathologic findings upon prostatectomy. The presence of biopsy PNI may have a role in further risk stratifying patients who meet expanded criteria for AS. UROLOGY ■■: ■■–■■, 2016. © 2016 Elsevier Inc.

Active surveillance (AS) has been increasingly adopted in response to the overtreatment of men with low-risk prostate cancer.[1] The strategy of AS programs is to identify patients with clinically indolent tumors and avoid or delay definitive treatment in these men.[2] Although the rationale for AS is well established, there is no consensus regarding the optimal characteristics of patients who should be managed by this strategy. The varied inclusion criteria in cohorts of men undergoing longitudinal study of AS reflect these varied definitions of insignificant disease, which are usually based on prostate biopsy characteristics and the level of prostate-specific antigen (PSA) or its derivatives, such as PSA density.[3-9]

The role of perineural invasion (PNI) in the selection of men for AS is unclear. Biopsy PNI has been associated with worse outcomes following definitive therapy.[10-12] Furthermore, when studied in patients undergoing AS, biopsy PNI was associated with both clinical and pathologic progression, suggesting that men with biopsy PNI may not be good candidates for AS.[13,14] Despite its lack of consideration in established selection criteria, biopsy PNI has been shown to influence selection of patients for AS in the clinical setting.[15] However, in patients who meet the most conservative criteria for AS, biopsy PNI has not been associated with adverse findings at radical prostatectomy, suggesting that, in highly selected patients, this pathologic finding should not exclude patients from this treatment option.[16,17]

Because of the uncertainty that remains regarding the role of biopsy PNI in selecting men for AS, we performed a study to evaluate the association of biopsy PNI with adverse pathologic findings on radical prostatectomy and biochemical recurrence following radical prostatectomy in patients who would have been candidates for AS. In

Financial Disclosure: *Bruce L. Jacobs is supported in part by the National Institutes of Health Institutional KL2 award (KL2TR000146-08), the GEMSSTAR award (R03AG048091), the Jahnigen Career Development Award, and the Tippins Foundation Scholar Award. He is also a consultant for Via Oncology.*

Funding Support: *Robert M. Turner II is supported in part by the* National Institutes of Health *Institutional TL1 award* (5TL1TR000145-10).

From the Department of Urology, University of Pittsburgh Medical Center, Pittsburgh, PA; the Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; and the Department of Urology, Fox Chase Cancer Center, Philadelphia, PA

Address correspondence to: Robert M. Turner II, M.D., UPMC Mercy Professional Building, 1350 Locust St., Suite G100A, Pittsburgh, PA 15219. E-mail: turnerrm@upmc.edu

Submitted: June 16, 2016, accepted (with revisions): November 2, 2016

http://dx.doi.org/10.1016/j.urology.2016.11.011
0090-4295

consideration of the varying selection criteria in patients offered AS, we performed our analyses in 2 cohorts of men—those who met strict criteria for AS and those who met expanded criteria.

MATERIALS AND METHODS

Study Population

The study population consisted of all 3084 men who underwent radical prostatectomy by a single surgeon (JBN) at the University of Pittsburgh Medical Center between November 1999 and July 2015 and were included in a prospectively populated and continuously maintained database. Those who received neoadjuvant androgen deprivation therapy (n = 42), were diagnosed with prostatic tissue obtained from transurethral resection (n = 11), had fewer than 6 biopsy cores (n = 54), and were missing data regarding the number of cores (n = 307), number of positive cores (n = 15), biopsy grade (n = 1), and pathologic grade (n = 3) were excluded from the analysis.

Two cohorts of men who met selection criteria for AS were further identified. The "strict" AS cohort was defined according to the Johns Hopkins experience[5] based on the Epstein criteria for AS,[18] namely, clinical stage T1c, biopsy Gleason 3 + 3 or less, PSA less than 10 ng/mL, PSA density less than 0.15 ng/mL/cm^3, and 2 or fewer positive biopsy cores with 50% or less involvement of any positive core. The "expanded" AS cohort was defined according to the University of Toronto experience,[4,19] namely, clinical stage less than T3, PSA of 10 ng/mL or less (15 ng/mL or less if age is greater than 70), and Gleason 3 + 3 disease or less (Gleason 3 + 4 or less if age is greater than 70).

Prostate volumes on transrectal ultrasound were not universally available as referring urologists routinely performed prostate biopsies. Thus, the pathologic prostate mass was used as a surrogate for clinical prostate volume in the determination of PSA density, as the 2 measurements are highly correlated (r = 0.81).[20] Bilateral extended pelvic lymphadenectomy was routinely performed. All prostate specimens were reviewed by fellowship-trained genitourinary pathologists at the University of Pittsburgh Medical Center. Postoperatively, patients were monitored with periodic clinical and PSA assessments.

Outcomes

The primary study outcome was adverse pathology at radical prostatectomy. Specifically, the presence of extraprostatic extension, pathologic upgrading, positive surgical margin, and lymph node involvement were considered. Pathologic upgrading was defined as pathologic Gleason 3 + 4 or higher for patients with biopsy Gleason 3 + 3, and pathologic Gleason 4 + 3 or higher for patients with biopsy Gleason 3 + 4. Major upgrading was defined as pathologic Gleason 4 + 4 or higher. Additionally, the diameter of the dominant tumor nodule and the percentage of the prostate specimen composed of cancer were considered. A secondary outcome was biochemical recurrence following radical prostatectomy, as defined as 2 successive postoperative PSA values of 0.2 ng/mL or greater.

The primary predictor was the presence of PNI on prostate needle biopsy. Biopsy PNI was defined as the histopathologic finding of circumferential or longitudinal tracking of prostate cancer cells along a nerve within the perineural space. The presence or absence of biopsy PNI was assessed in all biopsy specimens before radical prostatectomy and did not knowingly alter treatment selection or surgical technique. For purpose of comparison, men in each AS cohort were categorized into 2 groups according to the presence or absence of biopsy PNI.

Statistical Analysis

Demographic, clinical, and pathologic characteristics were compared between groups using t tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher exact tests for categorical variables. To assess for potential confounding, we performed additional analyses. First, logistic regression was used to assess whether performance of a nonstandard prostate biopsy (6-11 cores) confounded the relationship between biopsy PNI and outcomes. Second, we used logistic regression to assess whether the 2005 adoption of the International Society of Urological Pathology Consensus Conference on Gleason grading[21] confounded the relationship. In both cases, there were no substantial changes in the results, so we only report our primary findings.

Statistical analyses were carried out using R (version 13.2)[22] using the packages dpylr[23] for data manipulation and compareGroups[24] for descriptive tables. Statistical significance was defined as $P < .05$. The University of Pittsburgh Institutional Review Board approved the study (PRO0304058).

RESULTS

Strict AS Cohort

Baseline demographic, clinical, and biopsy characteristics of the study population are summarized in Table 1. A total of 596 men were identified who met strict criteria for AS, of whom 16 (3%) had biopsy PNI. In the strict cohort, men with biopsy PNI had greater comorbidity (P = .04) and were more likely to have 2 positive biopsy cores (63% vs 32%, P = .02) relative to men without biopsy PNI. No significant differences were identified with respect to patient age, race, body mass index, surgical year, preoperative PSA, PSA density, and the highest maximum percentage of cancer on biopsy.

Pathologic findings at radical prostatectomy are summarized in Table 2. In the strict cohort, there were no significant differences in extraprostatic extension (13% vs 7%, P = .30), pathologic upgrading (56% vs 42%, P = .37), median tumor volume (5% vs 5%, P = .86), or diameter of the dominant nodule (1.0 cm vs 1.1 cm, P = .24) between those men without and without biopsy PNI. Major pathologic upgrading, surgical margin involvement, and lymph node invasion were rare and only identified in men without biopsy PNI.

In the strict cohort, 12 men (2%) experienced biochemical recurrence at a median follow-up of 78 months (interquartile range 42-113 months). All men who recurred had no evidence of biopsy PNI.

Expanded AS Cohort

A total of 1197 men were identified who met expanded criteria for AS, of whom 102 (9%) had biopsy PNI. In the expanded cohort, men with biopsy PNI had higher clinical stage ($P < .001$), a greater number of positive cores ($P < .001$), higher maximum percentage of cancer in a single biopsy core ($P < .001$), and a larger proportion with biopsy Gleason 3 + 4 (5% vs 1%, P = .01) relative to men without biopsy PNI. PSA density was also higher in those patients with biopsy PNI (0.10 ng/mL/cm^3 vs 0.09 ng/mL/cm^3, P = .01). No significant differences were identified with