Baseline Perineural Invasion is Associated with Shorter Time to Progression in Men with Prostate Cancer Undergoing Active Surveillance: Results from the REDEEM Study

Daniel M. Moreira,* Neil E. Fleshner† and Stephen J. Freedland

From the Department of Urology, Mayo Clinic (DMM), Rochester, Minnesota, Division of Urology, Princess Margaret Hospital, University Health Network and Division of Urology, Department of Surgery, University of Toronto, Toronto (NEF), Ontario, Canada, Division of Urology, Department of Surgery and the Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center (SJF), Los Angeles, California, and Urology Section, Veterans Affairs Medical Center (SJF), Durham, North Carolina

Abbreviations and Acronyms

AS = active surveillance
BMI = body mass index
DRE = digital rectal examination
PCa = prostate cancer
PNI = perineural invasion
PSA = prostate specific antigen

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* Correspondence: Mayo Clinic, 200 First St. Southwest, Rochester, Minnesota 55905 (telephone: 507-284-2511; e-mail: moreira.daniel@mayo.edu).

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Purpose: We evaluated the association of perineural invasion with disease progression in men with prostate cancer on active surveillance.

Materials and Methods: We retrospectively analyzed the records of 302 men on active surveillance for low risk prostate cancer (T1c-T2a), Gleason 6 or less, 3 or fewer positive cores, 50% or less of any core involved and prostate specific antigen 11 ng/ml or less in the REduction by Dutasteride of clinical progression Events in Expectant Management (REDEEM) study. Patients underwent study mandated biopsies 18 and 36 months after enrollment. Disease progression was divided into pathological (4 or greater positive cores, 50% or greater core involvement, or Gleason greater than 6 on followup biopsy), therapeutic (any therapeutic prostate cancer intervention) or clinical (pathological or therapeutic progression). Time to disease progression was analyzed with Cox models adjusting for patient age, race, baseline prostate specific antigen, number of sampled and involved cores, tumor length and treatment.

Results: A total of 11 patients (4%) had perineural invasion on baseline biopsy. Perineural invasion was not associated with any baseline features (each $p > 0.05$). During the study clinical progression developed in 125 patients (41%), including pathological progression in 95. One, 2 and 3-year clinical progression-free survival for men with vs without perineural invasion was 82%, 27% and 27% vs 93%, 67% and 58%, respectively ($p < 0.05$). On multivariable analyses perineural invasion was associated with clinical (HR 2.39, 95% CI 1.16–4.94, $p = 0.019$) and pathological progression (HR 2.21, 95% CI 0.92–5.33, $p = 0.076$).

Conclusions: Among patients with prostate cancer on active surveillance perineural invasion was associated with an increased risk of clinical progression. The 2-year risk of clinical progression with perineural invasion was 73%. If these results are confirmed, patients with perineural invasion may not be good active surveillance candidates.

Key Words: prostatic neoplasms, disease progression, prostate-specific antigen, neoplasm invasiveness, risk

Perineural invasion is characterized by the presence of cancer infiltration in, around and/or through the nerves.[1] It is a distinct pathological entity that can occur in the absence of lymphatic or vascular invasion.[2] PNI is frequently identified in PCa.[3] Indeed, the prevalence of PNI in

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prostate specimens varies from 23% to 90% among men with PCa undergoing radical prostatectomy.[4–7] Moreover, data on surgical and radiotherapy cohorts indicate that PNI is present in 7% to 43% of prostate needle biopsies with PCa.[8]

Given its high prevalence, the clinical significance of PNI has been evaluated in numerous settings by various groups. The presence of PNI in radical prostatectomy specimens has correlated with several adverse pathological factors such as higher stage and grade but most studies failed to show any correlation between PNI and worse outcomes after adjustments for other well established prognostic features.[5–7] Conversely multiple studies have demonstrated a higher risk of biochemical recurrence after radical prostatectomy and radiotherapy, progression to metastatic disease and cancer specific mortality when PNI is seen in the biopsy tissue.[8–10] However, the clinical significance of PNI in men on AS is not well established. One study of patients being evaluated for AS showed that PNI in the diagnostic biopsy for PCa was associated with a higher rate of exclusion from AS due to disease progression (higher Gleason score and/or tumor volume) in the confirmatory biopsy done within 6 months.[11] Yet to our knowledge it remains unknown whether PNI is associated with worse outcomes in patients that are actually on AS. This is particularly important given that progressively more patients with PCa are being placed on AS today.[12]

Therefore, we evaluated the association of PNI with time to clinical progression (ie pathological or therapeutic progression) and pathological progression in men with PCa on AS enrolled in the REDEEM study.[13] Based on previous studies of men undergoing surgery or radiation we hypothesized that PNI would be associated with shorter time to progression.

MATERIALS AND METHODS

Study Sample

The REDEEM design was published previously.[13] Briefly, eligible men were 48 to 82 years old with clinically diagnosed (within 14 months before screening) low risk PCa (T1c-T2a) and Gleason score 6 or less (no Gleason pattern score 4 or greater) on AS, serum PSA 11 ng/ml or less and life expectancy greater than 5 years. Baseline biopsies had a minimum of 10 cores with fewer than 4 positive cores and less than 50% of any 1 core involved with PCa. Men were excluded from analysis if they had previous treatment for PCa with radiotherapy, chemotherapy or hormonal therapy, use of glucocorticoids (apart from inhaled or topical) within 3 months of screening or gonadotropin-releasing hormone analogues, prostate volume greater than 80 ml, previous prostatic surgery or severe benign prostatic hyperplasia symptoms, defined as I-PSS (International Prostate Symptom Score) 25 or greater, or 20 or greater if receiving α-blocker. Medical history was collected at baseline.

All men were randomized in double-blind fashion to receive orally dutasteride 0.5 mg or placebo daily. They were followed every 3 months for year 1 and every 6 months thereafter. A 12-core transrectal ultrasound guided prostate biopsy was obtained at 18 and 36 months, and at early study withdrawal when applicable. Central pathological review of all histological specimens, including baseline biopsies, was performed. PNI in baseline biopsies was coded as present or absent.

The study was approved by the institutional review board at each research site and all participants provided written informed consent. All 302 participants in REDEEM were included in the current study.

Statistical Analysis

The primary objective was to determine the association of baseline PNI (coded as present or absent) and time from study enrollment to clinical progression. Clinical progression was pathological (defined as 4 or more involved cores, 50% or greater of any core involved, or a Gleason pattern score 4 or greater) or therapeutic (defined as initiation of definitive treatment such as prostatectomy, radiation or hormonal therapy). On univariable analysis clinical progression-free survival was estimated and plotted using the Kaplan-Meier method and compared between patients with and without baseline PNI using the log rank test. On multivariable analysis the association of baseline PNI with clinical progression-free survival was tested with Cox proportional hazards regression models and summarized with the HR and 95% CI. Multivariable analyses were adjusted for baseline age (continuous in years), race (white or nonwhite) baseline PSA (continuous in ng/ml), baseline number of cores sampled (continuous), baseline number of cores involved (continuous), baseline tumor length (continuous in mm) and treatment arm (placebo or dutasteride).

The secondary objective was to determine the association of baseline PNI with time to pathological progression. This was analyzed as described for the primary objective. Patients in whom therapeutic progression developed (ie who underwent treatment in the absence of pathological progression) were censored at the time of treatment. Comparisons of covariates between those with and without baseline PNI were done with the Student t-test for continuous variables and the chi-square test for categorical data. All statistical analyses were performed using R 3.1.1 (https://www.r-project.org/) with $p < 0.05$ considered statistically significant.

RESULTS

Of the 302 patients in the study 294 (97%) were white. Mean ± SD baseline age was 65.0 ± 7.3 years and mean BMI was 28.6 ± 5.1 kg/m^2. A total of 61 men (20%) had a family history of PCa. Mean PSA was 5.9 ± 2.9 ng/ml and mean prostate volume was 43.6 ± 17.3 cm^3. Abnormal baseline DRE was identified in 33 patients (11%). The mean percentage of