Prostate Specific Antigen Velocity Risk Count Predicts Biopsy Reclassification for Men with Very Low Risk Prostate Cancer

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Purpose: Prostate specific antigen velocity is an unreliable predictor of adverse pathology findings in patients on active surveillance for low risk prostate cancer. However, to our knowledge a new concept called prostate specific antigen velocity risk count, recently validated in a screening cohort, has not been investigated in an active surveillance cohort.

Materials and Methods: We evaluated a cohort of men from 1995 to 2012 with prostate cancer on active surveillance. They had stage T1c disease, prostate specific antigen density less than 0.15 ng/ml, Gleason score 6 or less, 2 or fewer biopsy cores and 50% or less involvement of any core with cancer. The men were observed by semiannual prostate specific antigen measurements, digital rectal examinations and an annual surveillance biopsy. Treatment was recommended for biopsy reclassification. Patients with 30 months or greater of followup and 3 serial prostate specific antigen velocity measurements were used in primary analysis by logistic regression, Cox proportional hazards, Kaplan-Meier analysis and performance parameters, including the AUC of the ROC curve.

Results: Primary analysis included 275 of 668 men who met very low risk inclusion criteria, of whom 83 (30.2%) were reclassified at a median of 57.1 months. Reclassification risk increased with risk count, that is a risk count of 3 (HR 4.63, 95% CI 1.54–13.87) and 2 (HR 3.73, 95% CI 1.75–7.97) compared to zero. Results were similar for Gleason score reclassification (HR 7.45, 95% CI 1.60–34.71 and 3.96, 95% CI 1.35–11.62, respectively). On secondary analysis the negative predictive value (risk count 1 or less) was 91.5% for reclassification in the next year. Adding the prostate specific antigen velocity risk count improved the AUC in a model including baseline prostate specific antigen density (0.7423 vs 0.6818, $p = 0.025$) and it outperformed the addition of overall prostate specific antigen velocity (0.7423 vs 0.6960, $p = 0.037$).

Conclusions: Prostate specific antigen velocity risk count may be useful for monitoring patients on active surveillance and decreasing the frequency of biopsies needed in the long term.

Key Words: prostate, prostatic neoplasms, prostate-specific antigen, biopsy, risk

Abbreviations and Acronyms

AS = active surveillance
NPV = negative predictive value
PPV = positive predictive value
PSA = prostate specific antigen
PSAD = PSA density
PSAV = PSA velocity
RC = risk count

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ALTHOUGH an estimated 241,740 prostate cancer cases were diagnosed in 2012, about 50% were low grade (Gleason score 6 or less), of which greater than 90% were localized.[1,2] PSA screening is a major contributor to increased detection of early stage prostate cancer.[3] AS is an alternative

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to immediate intervention for low risk prostate cancer to decrease overtreatment with minimal or no compromise to oncological outcomes but it remains underused, lacking consistent criteria and triggers for intervention.[4]

PSA kinetics during AS have served as triggers for intervention in several programs and they are an attractive alternative to repeat biopsies.[5,6] However, recent evidence suggests that overall PSAV and PSA doubling time do not reliably predict adverse pathology findings.[7–9] Variability in PSA and followup duration may limit the value of a single overall PSAV calculation for patients on AS.

In 2007 a new concept called PSAV RC was proposed in which serial PSAVs are calculated and the number of times that they pass a threshold are counted to tabulate a score.[10,11] PSAV RC was recently validated in a screening cohort, demonstrating an eightfold increased risk of prostate cancer and a greater than fivefold increased risk of Gleason score 8 or greater disease for a RC of 2 vs 1 or zero.[12] To our knowledge the usefulness of PSAV RC in patients on AS who already carry a diagnosis of prostate cancer has not been evaluated.

Disease misclassification is a significant concern when determining eligibility for AS. Biopsy criteria and the number of cores are directly related to the sampling error rate.[13,14] Under grading may occur in up to a third of patients.[15] The initial diagnostic biopsy may not capture the correct grade or extent of disease, raising the question of whether higher grade disease on subsequent biopsy or prostatectomy is due to true disease progression or misclassification.[16] At our institution annual prostate biopsy results are used to determine disease reclassification and recommend curative therapy for very low risk prostate cancer.

We investigated an AS cohort beyond the initial misclassification period to determine whether PSAV RC is associated with biopsy reclassification of disease and whether it might represent a clinically useful measure for monitoring patients. We also evaluated the prognostic usefulness of the temporally earliest PSA information and compared model performance with that in addition to PSAV RC.

MATERIALS AND METHODS

Study Cohort

Since January 1995, older men with very low risk prostate cancer who present to our institution have been advised that AS is an alternative to immediate intervention.[17] As previously described by Epstein et al, inclusion criteria for very low risk prostate cancer include clinical stage T1c disease, PSAD less than 0.15 ng/ml and favorable characteristics on needle biopsy (Gleason score 6 or less, 2 or fewer biopsy cores with cancer and 50% or less involvement of any core with cancer).[18] With institutional review board approval and appropriate informed consent from all participants we observed men by semiannual serum PSA measurements and digital rectal examinations as well as annual extended 12-core or greater surveillance biopsy. Curative therapy was recommended upon disease reclassification, defined as surveillance biopsy with unfavorable pathology findings.

The primary analysis included patients on AS for at least 30 months without biopsy reclassification in whom 3 serial PSAVs were calculated using linear regression (fig. 1).[19,20] We selected 30 months to allow for time for 2 surveillance biopsies in all patients to minimize biopsy misclassification and enable sufficient followup for 3 serial PSAV calculations. Secondary analysis was done in patients with less than 30 months of followup, which allowed for only 1 or 2 serial PSAVs to be calculated. Finally, we analyzed early PSA data while on AS, looking at the first 2, 12-month and 24-month windows after diagnosis in

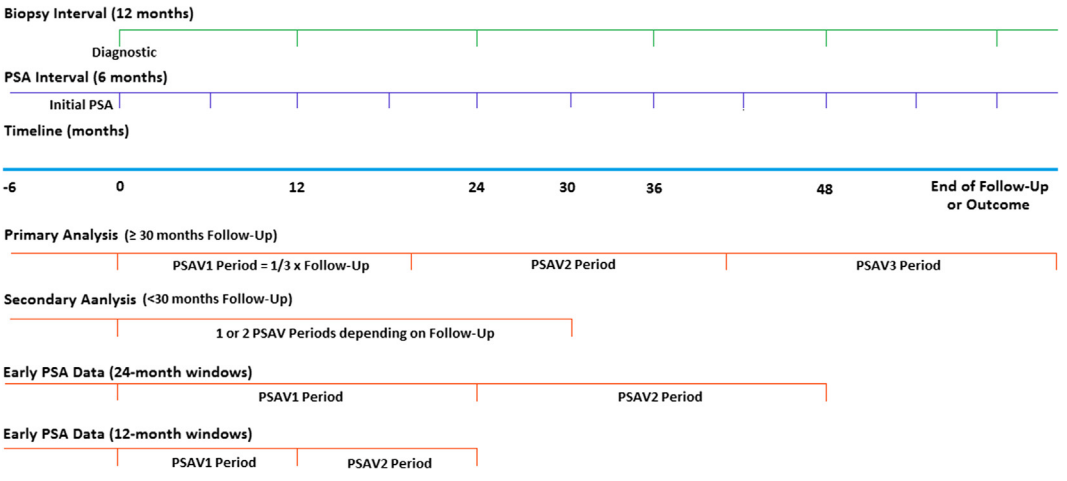

Figure 1. Study design shows timing of biopsies, PSA testing and periods for successive PSAV calculations 1 to 3 (*PSAV1*, *PSAV2* and *PSAV3*, respectively) in Johns Hopkins AS Program from 1995 to 2012.