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Prostate Cancer

Refined Analysis of Prostate-specific Antigen Kinetics to Predict Prostate Cancer Active Surveillance Outcomes

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Abstract

Background: For men on active surveillance for prostate cancer, utility of prostate-specific antigen (PSA) kinetics (PSAk) in predicting pathologic reclassification remains controversial.
Objective: To develop prediction methods for utilizing serial PSA and evaluate frequency of collection.
Design, setting, and participants: Data were collected from men enrolled in the multicenter Canary Prostate Active Surveillance Study, for whom PSA data were measured and biopsies performed on prespecified schedules. We developed a PSAk parameter based on a linear mixed-effect model (LMEM) that accounted for serial PSA levels.
Outcome measurements and statistical analysis: The association of diagnostic PSA and/or PSAk with time to reclassification (increase in cancer grade and/or volume) was evaluated using multivariable Cox proportional hazards models.
Results and limitations: A total of 851 men met the study criteria; 255 (30%) had a reclassification event within 5 yr. Median follow-up was 3.7 yr. After adjusting for prostate size, time since diagnosis, biopsy parameters, and diagnostic PSA, PSAk was a significant predictor of reclassification (hazard ratio for each 0.10 increase in PSAk = 1.6 [95% confidence interval 1.2–2.1, $p < 0.001$]). The PSAk model improved stratification of risk prediction for the top and bottom deciles of risk over a model without PSAk. Model performance was essentially identical using PSA data measured every 6 mo to those measured every 3 mo. The major limitation is the reliability of reclassification as an end point, although it drives most treatment decisions.
Conclusions: PSAk calculated using an LMEM statistically significantly predicts biopsy reclassification. Models that use repeat PSA measurements outperform a model incorporating only diagnostic PSA. Model performance is similar using PSA assessed every 3 or 6 mo. If validated, these results should inform optimal incorporation of PSA trends into active surveillance protocols and risk calculators.
Patient summary: In this report, we looked at whether repeat prostate-specific antigen (PSA) measurements, or PSA kinetics, improve prediction of biopsy outcomes in men using active surveillance to manage localized prostate cancer. We found that in a large multicenter active surveillance cohort, PSA kinetics improves the prediction of surveillance biopsy outcome.

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1. Introduction

Given the prolonged natural history and indolent behavior of most low-risk prostate cancers [1], active surveillance (AS) has been developed as an alternative to immediate treatment. Surveillance is now recognized as a preferred strategy for low-risk disease [2], and is offered to a large and growing proportion of men, both in the USA [3,4] and internationally [5]. While substantial variation persists in terms of eligibility criteria for surveillance, follow-up intervals, and triggers for intervention, all AS protocols are based principally on repeated prostate-specific antigen (PSA) measurements and periodic rebiopsy [2].

However, it remains unclear how to collect and interpret serial PSA data optimally in the AS setting. In most centers, PSA is collected quarterly, with the goal of identifying men with a rapid PSA rise, which may signify aggressive disease. However, studies to date have not shown analyses of PSA kinetics to be informative in most cases. In multiple cohorts, PSA kinetics consistently failed to predict reclassification based on biopsy parameters (ie, increase in biopsy Gleason grade and/or tumor volume) [6–8]. In the prospective, multicenter Canary Prostate Active Surveillance Study (PASS), PSA doubling time (PSADT) of <36 mo was originally a criterion for progression, but since consistently few men met this threshold it was dropped from the protocol [9].

Limiting factors in most AS cohorts reporting outcomes are the relatively short duration of follow-up and limited longitudinal PSA data. As the PASS cohort has matured with longer follow-up, additional PSA measurements, and more reclassification events, we have an opportunity to determine the extent to which PSA kinetics might facilitate improved decision making for men on surveillance for low-risk prostate cancer. We also aimed to determine whether quarterly PSA measurements are necessary for accurate assessment of PSA kinetics or whether semiannual measurement would be sufficient.

2. Patients and methods

The Canary PASS is a multicenter, prospective cohort study enrolling men on AS at nine North American centers. Men eligible for AS provide informed consent under institutional review board supervision (clinicaltrials.gov NCT00756665). In PASS, PSA is measured every 3 mo, clinic visits occur every 6 mo, and ultrasound-guided biopsies are performed 6–12 mo after diagnosis, 24 mo after diagnosis, and then every 2 yr. Other tests, including magnetic resonance imaging, are performed at the clinicians' discretion; however, as enrollment started in 2008, the majority of men did not undergo these procedures. For the current study, participants were enrolled before February 2016 and had diagnostic Gleason grade $\leq 3+4$ and <34% of biopsy cores involved with cancer, no history of 5α-reductase inhibitor (5ARI) use, and at least one PSA and one biopsy following diagnosis. The primary outcome was tumor reclassification, defined as an increase in primary or secondary Gleason grade, or an increase in tumor volume to ≥34% of total biopsy cores involved. Tumor risk at diagnosis was summarized using the validated Cancer of the Prostate Risk Assessment (CAPRA) score [10].

2.1. Statistical analysis

PSA may be measured irregularly during AS and is characterized by within-individual random variation, which may attenuate associations between PSA kinetics and clinical outcomes. To study longitudinal PSA measurements as predictors of reclassification while accommodating these complicating factors, a two-stage procedure was used [11,12]. Through this process, we derived a novel PSA kinetic parameter (designated PSAk), which we treated like a biomarker, and our approach conformed to the REMARK criteria for novel biomarkers [13].

First, we calculated PSAk using a linear mixed-effect model (LMEM), in which the natural logarithm of PSA (ln[PSA]) was modeled as a linear function of time since diagnosis, with a random intercept indicating the individual-specific ln(PSA) at diagnosis and a random slope reflecting the individual-specific rate of change over time. PSAk for each participant based on all his PSA measurements from diagnosis to a specific observation time was derived using the best linear unbiased predictor (BLUP) estimator from the LMEM (see the Supplementary material, Methods). Intraclass correlation (ICC) was calculated to assess how much of the variability in PSA was explained by between-participant variance compared with total variance. A high ICC indicates strong correlations among PSA measurements from the same individual.

Two other approaches for calculating PSA kinetics were considered: a linear regression model using all the PSA measurements from diagnosis to an observation time (simple PSAk [PSAkS]), and a slope change using two PSA measurements closest to and including the observation time (restricted simple PSAk [PSAkRS]). Models were adjusted for prostate size.

Second, Cox proportional hazards (PH) models were used to determine the risk of future reclassification as a function of covariates at each observation time. The outcome was defined as time from each PSA measurement to reclassification or censoring. Participants were censored at treatment, last study contact, or 2 yr after biopsy; the latter criterion was included to control for patients who do not undergo ongoing serial biopsies, and therefore may accrue long-term follow-up but do not have the possibility of meeting the reclassification outcome. Individual-specific PSAk at each measurement time estimated from stage 1 was the key covariate. Other covariates considered were the following: age, ln(prostate size), ln(observation time since diagnosis), diagnostic Gleason (3 + 3 or 3 + 4), percent of positive biopsy cores, number of biopsies since diagnosis (0, 1, 2, 3, or 4+), negative biopsy since diagnosis, recent biopsy result (cancer vs no cancer), and ln(diagnostic PSA). Tests for proportionality confirmed that the PH assumptions were valid.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with robust variance estimates to account for correlations from multiple observations from the same individual. Model fit was compared using the Akaike information criterion (AIC); a smaller AIC indicated better goodness of fit. Nonsignificant variables were backward eliminated using a p value cutoff of 0.05.

To address whether our results were biased by an increase or a decrease in PSAk that influenced the decision to undergo or delay a biopsy, several steps were taken. Timing of each biopsy was defined as "on time," "early," or "late" based on the PASS protocol. Multinomial regression analyses were used to determine whether biopsy timing was associated with PSAk. Three different sensitivity analyses were performed: compliant participants only (all biopsies needed to be compliant to the protocol), compliant biopsies only (only data preceding on-time biopsies were included), and adjusted event or censor time (early and late biopsies were adjusted by a randomly selected time within the "on-time" window). Further details are provided in the Supplementary material.

To assess the performance of the multivariable model incorporating PSAk, the Cox PH model was used to calculate individual risk of having a

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