Variation of Serum Prostate-Specific Antigen in Men with Prostate Cancer Managed with Active Surveillance

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Abstract

To describe fluctuations in PSA levels in men managed with AS to determine if a single PSA increase is a consistent measure to trigger intervention.

We evaluated data on 541 men on AS from 1995 through 2011.

PSA variation was described by studying the Kaplan-Meier probability of patients’ PSA levels reaching 4 or 7 ng/mL, going below those thresholds, and then rising to those thresholds again.

We also examined PSA variation by calculating the Kaplan-Meier probability of a PSA change followed by an equal or greater change in the opposite direction.

We analyzed data on 541 AS patients with a median of 8 PSA measurements (IQR, 6–12) on AS for a median of 4 years (IQR, 2–6).

The 5-year estimate of the probability of reaching a threshold PSA of 7 ng/mL was 40% (95% CI, 35%–46%) and the 5-year estimate of subsequently falling below this threshold was 90% (95% CI, 82%–95%).

The 5-year estimate of a PSA direction change was 95% (95% CI, 93–97%) overall and 56% (95% CI, 51%–61%) for PSA direction changes of ≥1 ng/mL.

We observed a high probability of variability in PSA levels for men on AS.
- The probability of changes in PSA, defined by an increase to specified thresholds or a rise >1ng/mL within 6 months and subsequent decrease of equal or greater value on a subsequent measurement, increases over time.

- Therefore, a single change in PSA level is not a reliable endpoint for men on AS.

**Keywords**
prostate cancer; active surveillance; prostate specific antigen

**Introduction**

In the last two decades, a man’s lifetime risk of prostate cancer diagnosis has increased from 7% to 17%, with 58% of newly diagnosed cases classified as low-risk.\(^1,2\) The data from randomized studies in contemporary populations screened for prostate cancer provide little evidence that treatment improves survival in men with low-risk tumors.\(^3\) Observational studies support managing disease in these men with active surveillance (AS) and safely delaying curative treatment until there is evidence of cancer progression.\(^4\) Accordingly, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Prostate Cancer recommends AS for men with very-low-risk cancer and for many men with low-risk cancer, and AS is increasingly being adopted by major cancer centers.\(^5,6\) Clinical parameters to characterize an increased probability of high-risk disease and trigger immediate treatment for men on AS are actively being studied.

Published studies have set eligibility criteria for AS based on serum prostate-specific antigen (PSA), clinical stage determined by digital rectal examination, and prostate biopsy Gleason score.\(^7\) Triggers for intervention have been described as changes in these variables, and pathologic characteristics based on prostate biopsy The Gleason score remains the most predictive of significant cancer after radical prostatectomy.\(^8\) However, PSA testing is non-invasive, highly predictive of advanced prostate cancer, and, therefore, included in every AS protocol published.\(^9\) Despite evidence that PSA velocity does not predict reclassification to higher-risk disease on serial biopsy for men on AS, it remains a significant source of anxiety for men managed with AS and represents a diagnostic dilemma for physicians.\(^10,11\) These studies suggest that the natural biologic variation in PSA may occur in men on AS in the short term. The variability of serum PSA in men without a diagnosis of prostate cancer was characterized in a landmark longitudinal observational cohort study of men participating in the Polyp Prevention Trial.\(^12\) In this unscreened population, the authors discovered that 44% of men with a PSA level above 4 ng/mL had a normal PSA finding at 1 or more subsequent visits. However, the variability in PSA values for men with prostate cancer on AS remains understudied.

We investigated a large cohort of men on AS whose serum PSA values were collected in a prospective clinical database during a 15-year period. Our objectives were to describe the variation of PSA levels and determine whether fluctuations in PSA levels suggest that a single PSA increase is unreliable to trigger early intervention, either biopsy or immediate treatment. To the best of our knowledge this is the first study descriptively detailing the PSA variation measured longitudinally in men on AS. Our study specifically addresses a
clinically relevant question for patients and physicians: does a single elevation in PSA signal a continuing rise over time?

**Materials and Methods**

After institutional review board approval, we examined the records of patients with PCa who underwent AS at a tertiary cancer center from 1995 through 2011. Among these patients, we selected patients who had PSA scores ≤10 ng/mL, clinical stage T1–T2a, and any Gleason score ≤6 or 1 core with a secondary Gleason pattern 4. Within 6 months of initial diagnosis, every patient considering AS underwent a confirmatory biopsy at our institution to establish eligibility before enrolling in AS.

Patients were followed semiannually with digital rectal examination (DRE) and PSA measurements as previously reported. It was routinely recommended that a follow-up biopsy be performed 12–18 months following the start of AS and subsequently every 2–3 years or as prompted by the physician based on changes in clinical parameters, including DRE or imaging. Surveillance imaging, consisting of multiparametric MRI (mpMRI), was usually performed every 2–3 years. Curative treatment was recommended when a patient no longer met the previously described/AS eligibility criteria, specifically, an increase in tumor grade (biopsy Gleason score >6) or volume (more than 1 biopsy core of secondary Gleason pattern 4) or changes on mpMRI suggestive of disease progression, including extracapsular extension or pelvic lymphadenopathy. Importantly, a rising PSA level was only used to recommend repeat biopsy rather than to trigger curative treatment. However, as patients may insist on treatment or otherwise deviate from AS when faced with high PSA variation or steadily rising PSA, the variation that we would be able to observe in this study would be truncated: true variation in men eligible for AS may be much higher.

In order to make reliable estimates of PSA variation, we excluded men if they had fewer than 4 PSA results available from the time of diagnosis until their last follow up. We also excluded the PSA measurement closest to the time of surgery or radiation for those patients who received delayed treatment after AS because we were interested in evaluating PSA variation during AS. The scope of our study was to describe PSA variation in men who continue surveillance. We only assessed data points within the period when the patients had not been reclassified, which explains why the PSA prior to treatment was excluded. We intended to illustrate how frequent PSA variation is in men who were strictly on AS without evidence of disease reclassification. Based on these criteria, 135 patients had too few PSA measurements available and were excluded from our study, leaving a cohort of 541 patients.

PSA variation was described as the probability of patients’ PSA levels reaching, dropping, and then rising again to specific thresholds over time. These thresholds were chosen a priori to provide relevant clinical context to our results. The majority of patients on AS have a PSA between 4ng/mL and 10ng/mL; therefore, physicians and patients must deal with changes in PSA that occur within this range. We studied the Kaplan-Meier probability of patients’ PSA levels reaching, dropping and then rising again to 7 ng/mL. We chose this threshold as it is the midpoint between the biopsy threshold (4 ng/mL) and an accepted criterion for intermediate-risk disease (≥10 ng/mL). We assumed that variation around 7 ng/mL would be
similar to variation around the variation around 10 ng/mL. We repeated this analysis for the biopsy threshold of 4 ng/mL. We also examined PSA variation by calculating the Kaplan-Meier probability that a total change in PSA across consecutive measurements was immediately followed by a total change in the opposite direction of equal or greater magnitude over consecutive PSA measurements, from the time of enrollment into AS. Importantly, this method is sensitive to any change in PSA direction and may indicate the natural variability of different PSA assays. To determine large variation, we then calculated the Kaplan-Meier probability of a total change of 1 ng/mL or greater that was immediately followed by a change of equal or greater magnitude in the opposite direction across consecutive measurements. The PSA level of a single patient in our study is shown in supplementary Figure 1a to demonstrate how these four measures of PSA variation were defined. Finally, to explore the pattern of PSA variation, we investigated the association between patients' first PSA on AS and the probability of a total change of 1 ng/mL or greater that was immediately followed by an equal or greater change in the opposite direction using a Cox proportional hazards model. We then calculated the Kaplan-Meier probability of this event stratifying by patients whose first PSA on AS was below 4 ng/mL, patients with a first PSA between 4 and 7 ng/mL, and patients with a first PSA greater than 7 ng/mL. For these same baseline PSA groups, we also calculated the percentage change in PSA tests taken no more than 6 months apart.

Results

The initial cohort included 676 patients whose prostate cancer was managed with AS from 1995 through 2011. After excluding patients with less than 4 PSA measurements, we studied 541 patients managed with AS for a median of 4 years (IQR, 2–6) with a median of 8 PSA measurements (IQR, 6–12) and a median PSA of 4.3 ng/mL (IQR, 2.78–6.22) at commencement of AS. Clinical characteristics of these men are shown in Table 1. Among patients with at least 4 PSA measurements, the Kaplan-Meier estimate of the probability of receiving curative treatment within 5 years of starting AS was 14% (95% CI, 11%–18%).

In our cohort of 541 patients, 445 patients started AS with a PSA below 7 ng/mL. Among these patients, the 1-year estimate of the probability of a patient's PSA reaching or exceeding 7 ng/mL was relatively low at 12% (95% CI, 9%–16%) but increased to 40% (95% CI, 35%–46%) by 5 years (supplementary Table 1a). However, we found that patients who reached a PSA of 7 ng/mL while on AS were extremely likely to see their PSA drop below the threshold with a 1-year estimate of 76% (95% CI, 68%–83%) and a 5-year estimate of 90% (95% CI, 82%–95%). However, patients whose PSA reached the threshold once were more likely to see their PSA reach this threshold a second time, as shown in Table 2. Similar results were found for the PSA threshold of 4 ng/mL among the 235 patients who started AS with a PSA below 4 ng/mL. The Kaplan-Meier curves for these events are shown in the supplementary files Figure 1b.

Examining PSA direction changes, the 1-year estimate of the probability of a PSA change followed by a change of equal or greater magnitude in the opposite direction was 27% (95% CI, 24%–31%), increasing to 95% by 5 years (95% CI, 93%–97%), as shown in Table 2. The Kaplan-Meier estimates for the probabilities of seeing a large PSA direction change in 1 or 5
years is somewhat lower at 10% (95% CI, 7%–12%) and 56% (95% CI, 51%–61%) respectively. The Kaplan-Meier curves for these events are shown in Figure 1.

We examined the probability of a large change in PSA direction stratified by the PSA value at the start of AS. We used a Cox proportional hazard model to determine if a patient’s initial PSA value was associated with a large change in PSA (≥1ng/mL) during AS. We found that initial PSA was significantly associated with an increased probability of a large PSA direction change (HR 1.11, 95% CI 1.08, 1.14, p<0.0001). The five year probability that a large PSA direction change is observed for men with a PSA value below 4ng/mL, between 4 and 7ng/mL, and greater than 7ng/mL is 32% (25%, 40%), 70% (62%,78%), and 82% (72%, 91%), respectively.

Finally, we illustrated in a clinically meaningful method the percentage change in PSA tests taken no more than 6 months apart, stratified by baseline PSA (Figure 2). Among the 518 patients in this analysis, 179 (35%) observed a percentage change of 50% or higher over follow up.

**Discussion**

We studied a large cohort of men with prostate cancer managed with AS and described the longitudinal changes in serum PSA strictly during the period of surveillance. We analyzed the magnitude and direction of PSA variation over time in men without evidence of disease reclassification during the study period. We observed considerable variability in serum PSA values for individual men and discovered that the probability of changes in PSA direction increased over time. These results suggest that a single PSA value should not be used to inform decisions regarding diagnostic prostate biopsy or radical treatment because additional changes in serum PSA are likely be observed with continued follow up. Our study will inform physicians and patients on the observed variability of serum PSA during active surveillance, thereby mitigating anxiety and possibly reducing the number of prostate biopsies triggered by an isolated PSA increase. The purpose of our study was not to determine the appropriate time for a follow-up PSA measurement; however, serum PSA is routinely measured every 6 months according to our institutional AS protocol.

The prognostic utility of PSA to determine disease progression for men on AS has been challenged based on observational studies. In a retrospective study exploring post-prostatectomy pathology findings of men with prostate cancer classified as intermediate or high risk based on a single PSA value, an elevated PSA measurement in the setting of other low-risk features did not significantly increase the risk of adverse pathologic and oncologic outcomes.14 In addition, a study examining PSA kinetics in a select cohort of men with low-risk, low-volume prostate cancer on AS did not find PSA velocity or PSA doubling time to predict biopsy-determined progression. These findings are complemented by high-quality observational data in men who were biopsied annually rather than in response to PSA changes, mitigating ascertainment bias.10 Although these results suggest PSA is an unreliable marker of disease progression, long-term data are not yet available to determine if PSA variability predicts cancer-specific mortality. Our study supports these findings by describing significant variability in longitudinally measured PSA and establishing that a
single PSA value is not valid as a trigger for prostate biopsy or definitive treatment in the short term.

In addition, we observed that the value of PSA at initiation of AS was associated with the probability that a large change in PSA would be measured during follow-up. Although variation in consecutive PSA measurements can be observed between different commercial assays, our cohort consisted of men followed at a single institution with PSA measured using a consistent assay.\textsuperscript{15} Our longitudinal data demonstrating variation during consecutive measurements are consistent with previous studies examining PSA changes in men without a diagnosis of prostate cancer.\textsuperscript{12} Furthermore, our observation that the initial PSA level is associated with the magnitude of change supports previous studies that describe a mean variation of approximately 15\% in measurements of total PSA for men older than 50 years of age.\textsuperscript{16}

Currently, there is no single standardized policy of follow-up for men managed with AS. In most cases, patients are examined quarterly or biannually with a PSA measurement and digital rectal exam and upgrade in Gleason pattern determined by prostate biopsy is used to define disease progression and recommend treatment. However, indications for recommending a prostate biopsy are not well-defined. Therefore, an isolated increase in PSA would trigger prostate biopsy and the implications of recommending another follow-up visit with a confirmatory PSA measurement has significant public health considerations. If the majority of men on AS who experience an isolated increase in PSA have a change in PSA equal or greater in magnitude on subsequent testing, then multiple repeat prostate biopsies and consequent risks of infections would substantially decrease.\textsuperscript{13} Other important benefits could be reducing anxiety among men on AS who would be subjected to less prostate biopsies and providing reassurance that PSA changes in the short term can be expected and AS for low risk prostate cancer is safe.

There are several limitations to our study. Our AS cohort was carefully selected, and the tools for disease classification have been refined during the study period with the inclusion of mpMRI to direct prostate biopsies; therefore the generalizability of our findings to other surveillance cohorts may be a limitation. The triggers for intervention were based on individual physician clinical judgment, and the time period set for surveillance prostate biopsies was variable. However, we excluded the last PSA value before disease reclassification or radical treatment to describe only PSA fluctuations during surveillance. As such, our study did not aim to evaluate the ability of PSA changes to predict reclassification. Instead, we sought to provide a better understanding of the natural history of PSA in men on AS that do not progress, by descriptively illustrating the expected PSA variation for men on AS. Also, we excluded men with less than 4 PSA measurements, potentially selecting for men on AS for a longer period. However, men who demonstrate disease progression soon after enrollment on AS are more likely to have had their cancer misclassified as low risk; subsequent prostate biopsy more likely represents disease reclassification than disease progression, based on the long natural history of prostate cancer.\textsuperscript{17} Importantly, every patient considering AS underwent a confirmatory biopsy within 6 months of initial diagnosis at our institution to establish eligibility before enrolling in AS. Finally, this is an observational, retrospective study, so true PSA variation in men eligible for

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AS may be much greater than we observed, as patients may insist on treatment counter to protocol when their PSA fluctuates too greatly or rises too high, regardless of biopsy results. In future studies, we plan to evaluate if differences in the frequency or magnitude of PSA direction change impact the risk for disease progression or adverse pathology after radical treatment.

Conclusions

In men with low-risk prostate cancer managed with AS, variability in consecutive PSA measurements is common. The majority of men experience changes in total PSA followed by changes of equal or greater magnitude on consecutive measurements within 5 years of starting AS. The probability of large PSA fluctuations increases with the initial PSA value. Prior to enrolling into AS, patients should be counseled about the expected variability in PSA measured during follow up, and physicians are obtaining a confirmatory PSA if a large increase is observed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>PSA</td>
<td>prostate-specific antigen</td>
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<tr>
<td>AS</td>
<td>active surveillance</td>
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<td>mpMRI</td>
<td>multiparametric MRI</td>
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<td>DRE</td>
<td>digital rectal exam</td>
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References

Figure 1.
Kaplan-Meier curves showing the probability of a) PSA direction change of any size and b) major PSA direction change of at least 1 ng/mL.
Figure 2.
Histogram showing maximum percentage change in PSA measured at least 6 months apart stratified by baseline PSA.
Table 1

Patient characteristics, n=541. Data presented as median (interquartile range) or number (percentage).

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>63 (58–68)</td>
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<tr>
<td>Baseline PSA (ng/mL)</td>
<td>4.3 (2.78–6.22)</td>
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<td>Gleason score at diagnosis</td>
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<tr>
<td>≤6</td>
<td>538 (99%)</td>
</tr>
<tr>
<td>7</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Number of PSA results available</td>
<td>8 (6–12)</td>
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<tr>
<td>Years on AS</td>
<td>4 (2–6)</td>
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<tr>
<td>PSA tests per year on AS</td>
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Table 2
Kaplan-Meier estimates of the probability of PSA direction change of any size and PSA direction change of at least 1 ng/mL.

<table>
<thead>
<tr>
<th>Years from beginning AS</th>
<th>Any PSA Direction Change (N=541)</th>
<th>PSA Direction Change ≥1 ng/mL (N=541)</th>
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<tbody>
<tr>
<td></td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
</tr>
<tr>
<td>1</td>
<td>27% 24%–31%</td>
<td>10% 7%–12%</td>
</tr>
<tr>
<td>2</td>
<td>65% 61%–69%</td>
<td>25% 22%–29%</td>
</tr>
<tr>
<td>3</td>
<td>86% 82%–89%</td>
<td>39% 35%–44%</td>
</tr>
<tr>
<td>4</td>
<td>94% 91%–96%</td>
<td>50% 45%–55%</td>
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<tr>
<td>5</td>
<td>95% 93%–97%</td>
<td>56% 51%–61%</td>
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