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The Relationship Between Prostate Specific Antigen Change and Biopsy Progression in Patients on Active Surveillance for Prostate Cancer

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Abbreviations and Acronyms
AS = active surveillance
CaP = prostate cancer
JHU = Johns Hopkins University
PSA = prostate specific antigen
PSADT = PSA doubling time
PSAV = PSA velocity

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Purpose: We assessed whether an association exists between a change in prostate specific antigen and biopsy progression in men on active surveillance.

Materials and Methods: A cohort of patients undergoing active surveillance for prostate cancer was identified from the urological oncology database at our institution. Multivariate logistic regression was performed to determine whether prostate specific antigen velocity, defined as the change in ln(prostate specific antigen) per year, is associated with biopsy progression, defined as a Gleason upgrade or volume progression on repeat biopsy within 24 months of diagnosis.

Results: A total of 241 men with a mean ± SD age of 61 ± 7 years and mean prostate specific antigen 4.9 ± 2.2 ng/ml met study inclusion criteria. Median time to repeat biopsy was 10 months (IQR 6–13). Biopsy progression developed in 55 men (23%), including a Gleason score upgrade in 46 (19%), greater than 33% positive cores in 11 (5%) and greater than 50% maximum single core positive in 12 (5%). The median prostate specific antigen ratio per year was 1.0 (IQR 0.95–1.03), although 1 man had a ratio of greater than 1.26 (doubled over 3 years) and 7 had a ratio of less than 1/1.26 (halved over 3 years). On multivariate analysis prostate specific antigen doubling within 3 years was associated with a 1.4-fold increase in the odds of biopsy progression (OR 1.4, 95% CI 0.6–3.4, p = 0.46).

Conclusions: There is little change in prostate specific antigen during the first 24 months of surveillance in men with well staged, low risk prostate cancer. We believe that these findings highlight the importance of repeat biopsy during surveillance.

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

Prostate specific antigen based CaP screening has led to a significant increase in the detection of low grade, stage and volume CaP.¹ This is exemplified by the fact that the proportion of patients presenting with low risk disease has increased from approximately 30% in the 1990s to 50% in the 2000s.² Most of these men at low risk are actively treated despite evidence that many may never experience CaP related morbidity or mortality.³ AS is an established management strategy for low risk CaP that provides a potential solution to the concerns of overtreatment of indolent disease.⁴
Although strict criteria for enrollment in AS programs are currently being refined, there is consensus that the best candidates are men with PSA less than 10 ng/ml, clinical stage T1c or T2 disease, Gleason score 6 or less (no pattern 4 or 5) and a small disease volume on biopsy.\textsuperscript{5–7} Men who are older and/or have comorbid disease with limited Gleason 3 + 4 disease, ie a small component of pattern 4 and limited overall disease volume or higher PSA, may also be appropriate candidates according to recent reports.\textsuperscript{7} Groups at most institutions with large AS series use a combination of repeat biopsy characteristics (upgrading or volume increase) and PSA kinetics (PSAV or PSADT) as potential triggers for definitive treatment. At our institution approximately two-thirds of patients on AS who proceed to treatment do so after an increase in Gleason score or approximately two-thirds of patients on AS who proceed to treatment do so after an increase in Gleason score or Gleason 3 + 4 disease, ie a small component of pattern 4 and limited overall disease volume or higher PSA, may also be appropriate candidates according to recent reports.\textsuperscript{5}

Although the National Comprehensive Cancer Network recommends that PSAV greater than 0.75 ng/ml yearly or PSADT less than 36 months be considered as evidence of progression,\textsuperscript{8} there is some debate in the literature on whether PSA kinetics are a useful part of the surveillance strategy. While most initial reports showed an association with disease progression on biopsy,\textsuperscript{9–12} a recent study with followup approaching 3 years indicated no association between PSAV or PSADT and biopsy progression.\textsuperscript{13}

During the first 24 months of AS we determined the concordance between 2 measures commonly used for monitoring, including change in PSA and biopsy progression.

**MATERIALS AND METHODS**

Men with CaP who are enrolled prospectively into the institutional AS program at our institution were identified through our urological oncology database. The database is approved by the institutional review board to collect clinical, pathological and followup data on consenting patients. Our recommendations for AS include PSA less than 10 ng/ml, clinical stage T1c or T2, Gleason score 6 or less, 33% or fewer of at least 6 cores positive and no single core greater than 50%, although some men with features outside these parameters elect AS as the management strategy. Our surveillance regimen consists of serial PSA measurements at 3-month intervals and repeat 12-core prostate biopsies at 12 to 18-month intervals. Biopsy specimens are assessed by a genitourinary pathologist (JPS) and all outside biopsies are re-reviewed at our institution.

Study eligibility criteria included CaP diagnosed on transrectal biopsy, consent to research, participation in the AS protocol, a minimum of 6 cores taken at diagnostic biopsy and progression-free status at diagnosis. To be included in analysis patients had at least 2 PSA measurements in ng/ml during the interval from 1 year before diagnostic biopsy through the repeat biopsy date and at least 1 repeat prostate biopsy done between 3 and 24 months after the diagnostic biopsy. Biopsies performed less than 3 months after the diagnostic biopsy were considered confirmatory biopsies and the subsequent biopsy was considered the repeat biopsy, which was used in analysis. To enhance the independence of longitudinal assessments PSA measurements were required to be made at least 3 weeks apart. To examine whether the study cohort remained representative of the target population we compared demographic, clinical and pathological characteristics of excluded patients with those of the study cohort using the chi-square test for categorical variables and the t test for continuous variables.

The primary outcome of interest was discordance/agreement between biopsy progression and PSAV with PSAV defined as the change in ln(PSA) per year.\textsuperscript{14} Using a random effects model we modeled patient specific trajectories of ln(PSA) as a linear function of PSA measurement time with time ranging from 1 year before CaP diagnosis through the repeat biopsy date. Patient specific intercepts and slopes from this model estimated that ln(PSA\textsubscript{0}), the value at diagnosis and PSAV, respectively, in patient i = 1, . . . , 241 as ln(PSA\textsubscript{time,i}) = ln(PSA\textsubscript{0,i}) + PSAVi × timei.

In each patient exp(PSAV) estimated the ratio of later to earlier PSA values measured 1 year apart, eg at 1 year vs at diagnosis (PSAV). The equation, ln(PSA\textsubscript{time,i}) = ln(2 PSA\textsubscript{0,i}), estimated the value at the time that the patient diagnostic PSA doubled and the equation, PSADT = ln(2) PSAV, estimated the corresponding doubling time. This equation shows that on the natural logarithm scale there was a 1-to-1 correspondence between PSAV and PSADT, and the threshold of PSADT 3 years or less equated to PSAV 0.231 ln(ng/ml) or greater per year, or exp(PSAV) 1.26-fold or greater increase per year. For use as a regression covariate we divided PSAV by 0.231 to enhance interpretability. PSADT is meaningful in patients with increasing PSA since PSAV greater than 0 implies a worsening condition, while PSA halving time is meaningful in patients with decreasing levels since PSAV less than 0 implies an improving condition, where PSA halving time = ln(0.5)/PSAV.

Biopsy progression within 2 years of CaP diagnosis (1—yes and 0—no) was defined as an increase in grade (Gleason score increase to 7 or greater) or in volume (to greater than 33% of cores positive or greater than 50% of the maximum core positive).

To adjust for other covariates we examined the dependence of biopsy progression status on continuous PSAV using a logistic regression model. The model was adjusted for age, prostate volume, clinical stage, whether diagnostic biopsy was done at our institution, whether the case met JHU AS protocol criteria and time from diagnostic to repeat biopsy. JHU AS criteria require clinical stage T1c, PSA density less than 0.15 ng/ml/cm\textsuperscript{3}, 12-core diagnostic biopsy with Gleason 6 or less, involvement of 2 or fewer cores and 50% or less involvement of an individual core.\textsuperscript{13} We summarized model results using the OR, 95% CI and p value for each covariate. Statistical analysis was done with SAS® 9.1 and STATA® 11.0.
A total of 167 patients with a mean age of 63 met the additional study inclusion criteria defined.

Stage was T1c in 166 (69%) vs 112 (68%) (p = 0.88), clinical stage was T1c in 166 (69%) vs 112 (68%) (p = 0.46) and the median percent of core positive was 7% (IQR 4–15) vs 11% (IQR 7–17) (p = 0.70). Of included and excluded patients median prostate volume was 36 cc (IQR 25–46) vs 41 cc (IQR 28–59) (p = 0.06) did not meet these criteria, including 37 who underwent treatment without repeat biopsy, 58 with no repeat biopsy and no followup PSA, 2 with repeat biopsy but no followup PSA and 70 with followup biopsy more than 2 years after initial diagnostic biopsy. In study vs excluded patients median prostate volume was 36 (IQR 25–46) vs 41 cc (IQR 28–59) (p = 0.88), clinical stage was T1c in 166 (69%) vs 112 (68%) (p = 0.46) and the median percent of core positive was 7% (IQR 4–15) vs 11% (IQR 7–17) (p = 0.70). Of included and excluded patients 77 (44%) and 37 (43%) met JHU AS protocol criteria, respectively.

The final study cohort and excluded patients had several statistically significant differences that were not clinically relevant. The study cohort had lower mean PSA at diagnosis (4.9 ± 2.2 vs 5.5 ± 2.1 ng/ml, p < 0.01) but a greater median maximum percent of core positive (7%, range 4% to 15% vs 4%, range 0% to 10%, p < 0.01). However, it was clinically relevant that fewer patients underwent the initial diagnostic biopsy at our institution in the included than in the excluded cohort (45 or 19% vs 52 or 32%, p < 0.01). Our experience is that cancer upgrade occurs more often when diagnostic biopsy is done elsewhere. The latter 2 features suggest that the study cohort was at greater risk for biopsy progression.

In the study cohort the unadjusted median ln(PSA) change per year was 0 ln(ng/ml) (IQR −0.05–0.026, see figure), corresponding to a yearly PSA ratio of 1.0 (IQR 0.95–1.03). Results were based on a median of 4 PSA measurements per patient (IQR 3–5) collected during a median of 15 months (IQR 10–22) of followup. Only 1 patient had PSA doubling within 3 years (2.7 years) and 7 had a 50% decrease in PSA within 3 years (see figure). Progression upon initial repeat biopsy occurred in 55 men (23%) at a median followup of 10 months (IQR 6–13), including 46 (19%) with an increased Gleason score, 11 (5%) with an increase in the percent of positive cores to greater than 33% and 12 (5%) with an increase in the maximum single core positive to greater than 50%.

RESULTS

A total of 408 patients on AS were eligible for study, of whom 241 with a mean ± SD age of 61 ± 7 years met the additional study inclusion criteria defined. A total of 167 patients with a mean age of 63 ± 8 years (vs cohort patients p = 0.06) did not meet these criteria, including 37 who underwent treatment without repeat biopsy, 58 with no repeat biopsy and no followup PSA, 2 with repeat biopsy but no followup PSA and 70 with followup biopsy more than 2 years after initial diagnostic biopsy. In study vs excluded patients median prostate volume was 36 (IQR 25–46) vs 41 cc (IQR 28–59) (p = 0.88), clinical stage was T1c in 166 (69%) vs 112 (68%) (p = 0.46) and the median percent of core positive was 7% (IQR 4–15) vs 11% (IQR 7–17) (p = 0.70). Of included and excluded patients 77 (44%) and 37 (43%) met JHU AS protocol criteria, respectively.

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Untransformed unadjusted PSAV was 0.02 ng/ml yearly (IQR −0.66–0.69) in men without progression and −0.16 (IQR −0.79–0.20) in men with progression. The single patient with a 2-fold PSA increase had no biopsy progression but 1 of the 7 with a 50% PSA decrease showed biopsy progression.

On univariate analysis PSAV per 3 years was associated with slightly greater odds of progression, although the difference was not significant (OR 1.2, 95% CI 0.6–7.5, p = 0.22). The odds of progression after multivariate adjustment increased but again did not attain statistical significance (OR 1.4, 95% CI 0.6–3.4, p = 0.46, see table). Thus, PSA doubling within 3 years was associated with 1.4-fold increased odds of biopsy progression. Older men had significantly increased odds of biopsy progression (p = 0.02) while men with higher stage disease and longer times between biopsies had a nonsignificant increase. Men at lower risk, including candidates for the JHU AS protocol and patients in whom diagnostic biopsy was done at our institution, showed slightly lower odds of biopsy progression that were not statistically significant. Increasing prostate volume showed a statistically significant decrease in the odds of biopsy progression (p = 0.03).

DISCUSSION

In this cohort of men with well staged, low risk CaP it was striking how little change in PSA there was during the study period. Clearly biopsy progression can develop in the absence of a change in PSA. Since so few men had a significant PSA change, our esti-
mate of the association between PSAV and biopsy progression did not attain statistical significance, although it was clinically relevant. This held true for biopsy progression based on a composite of Gleason upgrade, increase in the percent of cores positive to greater than 33% or increase in the maximum percent core positive to greater than 50% as well as for Gleason upgrade alone. These results provide strong support to the need for biopsy in the first 24 months of surveillance regardless of PSA. The supporting role of serial PSA requires further investigation in men treated without biopsy progression to assess adverse pathological results that are unrecognized by biopsy.

Three prior studies showed a strong association between PSA kinetics and biopsy progression. Similar to these studies, we defined biopsy progression more broadly as a composite assessment of an increase in tumor volume and Gleason grade. We also tried to improve on several methodological issues by excluding patients with a long biopsy interval, not using PSA values obtained after repeat biopsy to calculate PSA kinetics and not using Cox regression to analyze biopsy progression, which is an infrequently measured variable.

However, our results do not strongly refute those presented in the recent series by Ross et al showing no association between PSAV and progression. Before that publication only 1 study failed to show an association between PSAV or PSADT and biopsy progression. An editorial accompanying the article by Ross et al stated that their results may have been due to the strict AS inclusion criteria used at their institution. The current study cohort is more generalizable to all patients at low risk who may elect AS rather than the approximately 44% who meet JHU criteria. Studies in the near future may be able to improve on several methodological issues by excluding patients who met our institutional criteria vs JHU criteria. Together these data suggest that surveillance in older patients should be similar to that in younger patients, at least during early followup. Furthermore, men with a larger prostate had lower odds of upgrading. Although we did not include PSA density due to possible collinearity between PSA and PSA kinetics, it supports its use in risk stratification in men with CaP who may elect AS. However, the ideal threshold value remains to be determined. There was a slight but nonsignificant difference in the odds of progression during 2 years between patients who met our institutional criteria vs JHU criteria.

Another critique was that selection bias may have led to the findings in the study by Ross et al since patients were excluded if they underwent treatment, although repeat biopsy showed no progression. This could occur due to adverse PSA kinetics. We did not use treatment without biopsy progression as an exclusion criterion in our study. The only patients excluded from our analysis had no followup PSA or repeat biopsy data available, or returned for repeat biopsy more than 2 years after diagnostic biopsy. We believe that comparison of the study cohort and excluded patients in the current study confirms that they were overall similar at baseline.

Although our results differ somewhat, we believe that our data support the final conclusions of Ross et al that PSA kinetics are insufficient to replace repeat biopsy. Within an average of approximately 1 year of postdiagnostic followup biopsy progression developed in 22% of our cohort, although no patient experienced PSA doubling within 1 year and only 1 showed doubling within 3 years. Thus, it is unlikely that PSA alone can be used in the surveillance of men with low risk CaP. We found evidence that men with a 50% PSA decrease after diagnosis, which may develop with surreptitious detection after PSA is measured during an inflammation or infection episode, are at low risk for biopsy progression. Although they still require biopsy, the PSA decrease allows them to forgo definitive treatment with increased confidence.

Older age was significantly associated with biopsy progression within 2 years of diagnosis. Older patients are known to be at increased risk for high grade disease compared with younger patients. Together these data suggest that surveillance in older patients should be similar to that in younger patients, at least during early followup. Furthermore, men with a larger prostate had lower odds of upgrading. Although we did not include PSA density due to possible collinearity between PSA and PSA kinetics, it supports its use in risk stratification in men with CaP who may elect AS. However, the ideal threshold value remains to be determined. There was a slight but nonsignificant difference in the odds of progression during 2 years between patients who met our institutional criteria vs JHU criteria. Studies in the near future may be able to look at biochemical recurrence-free survival between such groups.

The main limitation of this study and others is that biopsy progression is potentially a poor surrogate for hard outcomes such as metastasis and CaP specific mortality, which rarely develop in low risk cases. AS series still have few patients and short followup compared with studies of treated patients. The JHU subset in our series included only 73 patients and may have had limited power to detect a clinically significant difference. Verification bias may still have been possible, although our protocol does not include PSA kinetics as a trigger for repeat biopsy or treatment since some patients may use own PSA kinetics as a prompt for return clinic visits and, thus, biopsy, or for treatment before repeat biopsy. Finally, we did not include patients at intermediate risk in analysis since the outcome of interest was already present. Therefore, these results should not be generalized to those patients.

CONCLUSIONS

There is little change in PSA during the first 24 months of surveillance in men with well staged, low risk prostate cancer. We believe that these findings highlight the importance of repeat biopsy during surveillance.
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