Extended Followup and Risk Factors for Disease Reclassification in a Large Active Surveillance Cohort for Localized Prostate Cancer

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Purpose: Active surveillance to manage prostate cancer provides an alternative to immediate treatment in men with low risk prostate cancer. We report updated outcomes from a long-standing active surveillance cohort and factors associated with reclassification.

Materials and Methods: We retrospectively reviewed data on all men enrolled in the active surveillance cohort at our institution with at least 6 months of followup between 1990 and 2013. Surveillance consisted of quarterly prostate specific antigen testing, repeat imaging with transrectal ultrasound at provider discretion and periodic repeat prostate biopsies. Factors associated with repeat biopsy reclassification and local treatment were determined by multivariate Cox proportional hazards regression. We also analyzed the association of prostate specific antigen density and outcomes stratified by prostate size.

Results: A total of 810 men who consented to participate in the research cohort were followed on active surveillance for a median of 60 months. Of these men 556 (69%) met strict criteria for active surveillance. Five-year overall survival was 98%, treatment-free survival was 60% and biopsy reclassification-free survival was 40%. There were no prostate cancer related deaths. On multivariate analysis prostate specific antigen density was positively associated with the risk of biopsy reclassification and treatment while the number of biopsies and time between biopsies were inversely associated with the 2 outcomes (each $p < 0.01$). When stratified by prostate volume, prostate specific antigen density remained significantly associated with biopsy reclassification for all strata but prostate specific antigen density was only significantly associated with treatment in men with a smaller prostate.

Conclusions: Significant prostate cancer related morbidity and mortality remained rare at intermediate followup. Prostate specific antigen density was independently associated with biopsy reclassification and treatment while on active surveillance.

Key Words: prostatic neoplasms, prostate-specific antigen, disease progression, outcome assessment, biopsy

Abbreviations and Acronyms

5-ari = 5α-reductase inhibitor
ADT = androgen deprivation therapy
AS = active surveillance
BxD = biopsy density
BxR = biopsy reclassification
CAPRA = Cancer of the Prostate Risk Assessment
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = PSA density
RP = radical prostatectomy

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Prostate cancer is the second leading cause of cancer death in men in the United States.[1] However, in the PSA era many newly diagnosed cases are low risk and potentially indolent.[2,3] AS is a management strategy

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involving PCa monitoring while delaying or avoiding definitive treatment.[4] Many published studies have demonstrated the short-term safety of AS but more data are needed to determine the intermediate and long-term safety of AS.[5–7]

More than 40% of men diagnosed with PCa in the United States are considered to have low risk disease.[8] However, about a third of the men with apparently low risk cancer are reclassified into a higher risk category upon followup biopsy.[9–12] The ability to identify men with low risk PCa who are likely to be reclassified would clearly be beneficial. Men with higher risk disease could be treated while the disease was still curable while those with truly indolent disease could be spared additional followup testing, risk and anxiety.

At several institutions, including ours, groups have reported risk factors for reclassification during AS, including initial biopsy characteristics, PSA velocity, PSAD, repeat biopsy results and other factors.[13–19] PSAD at diagnosis is one of the few metrics associated with the risk of disease reclassification and adverse pathological features in many of these studies. However, the relationship between PSAD and risk may vary across PCa risk levels and prostate volumes.[20,21] How to use PSAD when advising men on AS is still unclear.

The AS study at our institution has been accruing patients since 1990. We report outcomes from one of the longest running AS cohorts in North America. We assessed PSAD and a novel metric, BxD (defined as the number of total biopsy cores divided by prostate volume) as potential predictors of outcome during AS. We also evaluated the performance of PSAD as a predictor of outcome in men who did not meet our strict criteria for AS and across a wide range of prostate volumes.

METHODS

At the Department of Urology at our institution a study of AS for PCa began in 1990. Patients who consent to prospective data collection under internal review board supervision and who undergo no active treatment for at least 6 months after the first diagnostic biopsy are included in analysis. Eligibility criteria and monitoring protocol have evolved with time. Currently strict AS criteria at our institution are diagnostic PSA 10 ng/ml or less, clinical stage T1/2, biopsy Gleason grade 3 + 3 or less, 33% or less positive cores and 50% or less tumor in any single core. Carefully selected men who do not meet strict eligibility criteria may be enrolled. Recommended monitoring includes quarterly PSA testing, semiannual transrectal ultrasound and annual biopsy. The first surveillance (ie confirmatory) biopsy is recommended within 12 months of diagnostic biopsy. Subsequent surveillance biopsies are recommended every 12 to 24 months based on clinical risk. Surveillance biopsy sessions at our institution include at least 12 cores with sampling from each sextant (medial and lateral) and the anterior gland. The primary trigger for treatment has been biopsy reclassification. Additional indications for discussion of treatment were patient anxiety, CAPRA risk reclassification and change in clinical stage. PSA kinetics alone did not serve as an indication for treatment.

We retrospectively reviewed clinical data on men enrolled in the AS study from 1990 to 2013, evaluating the entire cohort as well as subgroups that met strict eligibility criteria or underwent multiple biopsies. We described independent demographics (age, race/ethnicity, relationship status and smoking status) and clinical characteristics (5-ari use, diagnostic T stage, biopsy Gleason grade and volume, PSA and prostate volume). Clinical risk at diagnosis was calculated using CAPRA on a scale of 0 to 10 and classified using validated CAPRA groups, including low—0 to 2, intermediate—3 to 5 and high risk—6 to 10.[22] PSAD at diagnosis was calculated as PSA at diagnosis divided by prostate volume in cc as measured on confirmatory transrectal ultrasound. BxD was calculated as the total number of biopsy cores taken divided by prostate volume. Outcomes were time to BxR and time to active treatment. BxR was defined as an increase in Gleason grade of 3 + 4 or greater, more than 33% positive cores or more than 50% of positive tissue in a single core. Time to Gleason grade reclassification in men with Gleason 3 + 3 cancer was included as a separate outcome. Men in whom disease at diagnosis exceeded these parameters were not included in BxR analysis. Active treatment included RP, radiotherapy or ADT that began more than 6 months after enrollment in AS.

Cohort demographic and clinical characteristics were described with frequency tables. The Pearson chi-square test was used for categorical variables, and the mean and ANOVA were used for continuous variables. Life tables, Kaplan-Meier curves and log rank test were applied for univariate time to event analysis of the outcomes. PSAD and other factors associated with outcomes served as independent variables and were assessed by multivariate Cox regression adjusted for demographic and clinical characteristics. Smoking was included as a predictor of interest due to prior research indicating an association of smoking history with poor PCa outcomes.[23] PSAD was analyzed in 3 ways (as a continuous variable, as a log-transformed variable to normalize the distribution of values and as a categorical variable for ease of interpretation). Models were used to assess the entire cohort and the subset that met strict low risk criteria. Model covariates were evaluated for interitem correlations. To assess the potential interaction between PSAD and prostate volume analysis was stratified by prostate size, including small—less than 30, medium—30 to 45 and large—greater than 45 cc based on the cohort distribution of values. Two-tailed $p < 0.05$ was considered statistically significant. All analysis was done with SAS® 9.2.

RESULTS

A total of 1,075 men were enrolled in the AS cohort at our institution from 1990 to 2013, of whom

810 with at least 6 months of followup consented to research. Of these men 556 (69%) met strict criteria for AS and 685 have undergone repeat biopsy. Those with repeat biopsy were similar to the cohort as a whole (supplementary table, http://jurology.com/). Mean ± SD age at diagnosis was 62.0 ± 7.9 years, 87% of patients were white, 76% were married/partnered and 80% had never smoked. Median PSA was 5.3 ng/ml (IQR 4.1–7.4) and median PSAD was 0.13 ng/ml/cc (IQR 0.09–0.19). At initial biopsy 738 men (92%) had a Gleason score of 6 or less, 716 (92%) had 33% or less of cores involved and 616 (90%) had 50% or less of any individual core involved.

At a median followup of 60 months (IQR 36–91, maximum 19 years) there were no deaths due to PCa. Metastatic disease developed in 1 patient (0.12%). Five-year overall survival was 98%, treatment-free survival was 60% and BxR-free survival was 40%. Median time to treatment was 25 months (IQR 15–45) and median time to reclassification was 17 months (IQR 10–33). The treatment rate was 60% in men who did and did not meet strict AS clinical criteria. Of the 348 treated men 240 (69%) underwent RP, 98 (28%) received some form of radiotherapy and 10 (3%) received ADT. PSA recurrence-free survival was 97% 1 year after RP.

In the multivariate model adjusted for clinical risk and sociodemographics a decreasing interval between biopsy and PSAD were positively associated with the risks of treatment and BxR. Age was associated with the risk of BxR but not with the risk of treatment. PSA at diagnosis and BxD were not associated with the risk of BxR or of treatment (see table).

Increasing logPSAD was associated with the risk of treatment (HR 1.59, 95% CI 1.24–2.03) and the risk of BxR (HR 1.90, 95% CI 1.55–2.33, see table). Patients with a PSAD of 0.1 to 0.15 ng/ml/cc were more likely to be treated (HR 1.75, 95% CI 1.20–2.56) and reclassified (HR 1.67, 95% CI 1.23–2.26) than those with PSAD less than 0.1 ng/ml/cc. Associations were stronger in men with PSAD greater than 0.15 ng/ml/cc (treatment and BxR HR 2.15, 95% CI 1.46–3.16 and 2.14, 95% CI 1.56–2.94, respectively, see table). Factors associated with Gleason grade reclassification alone did not meaningfully differ from those associated with BxR as a whole.

The interaction of prostate size and PSAD was explored by stratified analysis across small (less than 30 cc), intermediate (30 to 45 cc) and large (greater than 45 cc) prostates. Among men with a small prostate logPSAD was significantly associated with treatment and BxR (HR 1.52, 95% CI 1.03–2.24 and 1.92, 95% CI 1.41–2.62, respectively). In men with a medium or large prostate logPSAD remained associated with BxR but it was not significantly associated with treatment (see table).

Multivariate Cox proportional hazards regression of categorical and continuous PSAD, and outcomes of active treatment and BxR in men on AS at our institution

	Active Treatment*		BxR†	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Categorical PSAD				
Age at diagnosis	1.00 (0.98–1.01)	—	1.02 (1.00–1.03)	<0.05
Race (white)	1.15 (0.74–1.76)	—	1.06 (0.74–1.50)	—
Unmarried/widowed	0.96 (0.71–1.30)	—	0.96 (0.74–1.25)	—
Smoking history	0.68 (0.48–0.97)	<0.05	1.03 (0.78–1.36)	—
5-ari Use	0.50 (0.28–0.87)	<0.05	0.90 (0.60–1.33)	—
Met strict AS clinical risk criteria	0.95 (0.71–1.28)	—	0.93 (0.71–1.21)	—
Total No. biopsies	0.44 (0.39–0.50)	<0.01	0.47 (0.42–0.54)	<0.01
PSA at diagnosis (ng/ml)	0.99 (0.95–1.03)	—	0.99 (0.96–1.02)	—
BxD	0.97 (0.62–1.52)	—	1.05 (0.66–1.66)	—
Mos between biopsies	0.94 (0.92–0.95)	<0.01	0.93 (0.92–0.94)	<0.01
Biopsy reclassification	6.31 (4.30–9.25)	<0.01	—	—
PSAD (ng/ml/cc):				
0.1–0.15 vs less than 0.1	1.75 (1.20–2.56)	<0.01	1.67 (1.23–2.26)	<0.01
Greater than 0.15 vs less than 0.1	2.15 (1.46–3.16)	<0.01	2.14 (1.56–2.94)	<0.01
Continuous PSAD (logPSAD)				
All pts	1.59 (1.24–2.03)	<0.01	1.90 (1.55–2.33)	<0.01
Prostate vol only (cc):				<0.01
Less than 30	1.52 (1.03–2.24)	<0.05	1.92 (1.41–2.62)	
30–45	1.26 (0.70–2.29)	—	2.01 (1.32–3.05)	
Greater than 45	1.65 (0.86–3.19)	—	2.21 (1.29–3.77)	

* Also adjusted for diagnosis year, diagnosis age, race (white), married/partnered, prior smoking history, meeting strict AS clinical risk criteria, total number of biopsies, PSA at diagnosis, biopsy density and biopsy reclassification.
† Also adjusted for diagnosis year, diagnosis age, race (white), married/partnered, prior smoking history, meeting strict AS clinical risk criteria, total number of biopsies, PSA at diagnosis and biopsy density.

DISCUSSION

The short-term safety of AS has been demonstrated in multiple cohorts with only rare occurrences of PCa related death or metastasis reported.[10,11,19,24] Fewer cohorts reportedly have a median followup of beyond 5 years.[5–7] Our results extend the median followup previously reported in this cohort from 3.6 to 5 years and include more than 200 men with followup beyond 7.5 years. During this extended followup PCa metastasis and hormone therapy remained rare events. This is notable since this cohort included 125 men who did not meet strict criteria for AS inclusion and 67 with a diagnostic Gleason score of greater than 6.

The inclusion of men who did not meet very low risk entrance criteria is similar to inclusions in the University of Toronto cohort.[5] However, in contrast to the current cohort, there were 5 PCa related deaths in the University of Toronto cohort at a median followup of 6.8 years. More recently 15 PCa related deaths were reported at a median followup

of 8.3 years and an additional 12 patients survived with metastasis.[25] European studies of cohorts with intermediate followup describe death and metastasis in men who received AS or deferred treatment, including 2 deaths among 471 patients at the Royal Marsden Hospital[6] and 1 death among 439 in the Göteborg cohort.[7] Although the goal of AS is to identify men with less aggressive disease and treat them before PCa dissemination, it is possible that with additional followup some patients in the current cohort may have metastatic disease and die of PCa. Indeed, in a recent modeling study Xia et al estimated that men with very low risk PCa were at 2.8% risk for death compared to 1.6% in those treated immediately.[26]

As the acceptance and use of AS increase, an important question is whether the outcomes observed in current academic cohorts apply to the population at large. A key difference between our cohort and others is that men could be enrolled before repeat biopsy at our institution. This approach may better reflect the experience of men seen outside academic AS cohorts since men in the community are biopsied by many providers using various techniques. Lack of rebiopsy before inclusion may in part explain the higher observed rates of treatment and BxR compared to those of other cohorts. Notably even when including men before repeat biopsy and men who did not meet strict AS entry requirements, ADT, metastasis and PCa death remained extremely rare events.

Efforts are ongoing to improve risk assessment in men diagnosed with low and intermediate risk PCa. While tools such as magnetic resonance imaging and genetic tumor profiling hold promise, they require further validation before they can be widely incorporated into AS management protocols.[27] Even when these tools are available, they must be interpreted in the context of other well established predictors of risk. The current study expands the association of PSAD with disease reclassification and treatment by including men at higher risk and examining associations across multiple prostate sizes. The finding that PSAD remained a strong predictor of BxR in men who did not meet strict AS criteria could be helpful when counseling such patients who are still considering AS.

In addition, PSAD may have value even in men with PSAD less than 0.15 ng/ml/cc since that group was at higher risk for BxR than those with PSAD less than 0.1 ng/ml/cc. This is consistent with the findings of Tseng et al, who observed that of patients with PSAD less than 0.15 ng/ml/cc those with PSAD greater than 0.08 ng/ml/cc were at twofold increased risk of reclassification.[14] Lastly, PSAD was associated with the risk of active treatment independent of BxR and other clinical factors.

We postulated that PSAD may perform differently at the extremes of prostate size for several reasons. PSA production by benign prostate tissue varies. It is possible that the amount of incremental PSA produced by benign prostate glands in enlarged prostates is not linearly related to prostate size and PSAD becomes less sensitive as prostate size increases.[28] In addition, while absolute PSA tends to increase with increasing tumor volume, larger tumors may make less PSA per cc tumor volume than smaller tumors.[20] However, in our cohort PSAD was associated with BxR for all 3 strata of prostate size, indicating that PSAD is useful across a range of prostate sizes.

It is also possible that biopsy may not be as effective at detecting clinically significant disease in larger prostates.[29] In this study we used the metric BxD to assess the impact of the number of biopsy cores relative to prostate size on AS outcomes and we found no association. BxD may be associated with longer term outcomes that we cannot assess without further followup.

We included the use of 5-aris on multivariate analysis to control for the effect of these medications on prostate size and PSA. While 5-ari was associated with treatment in our cohort, this may have been for reasons other than clinical progression since 5-ari use was not associated with BxR. Not enough men in this cohort were receiving 5-ari to separately assess the performance of PSAD in these men.

Other caveats should be noted. While the current cohort is one of the longest standing AS cohorts reported, accrual has increased with time. The median recruitment year was 2006 and median followup has been 5 years. Treatment of patients on AS has evolved with time, which could have affected the results of this analysis. For example, men enrolled later in the cohort were biopsied more frequently than those enrolled earlier, increasing the chances of BxR and treatment. Notably BxR and subsequent active treatment are anticipated to occur during AS. Longer term clinical outcomes such as PCa metastasis and death would be preferable measures of the oncologic efficacy of AS.[30] However, we used the surrogate outcomes of BxR and treatment due to the rarity of metastasis and the absence of PCa related deaths. Also, since a PSA threshold of less than 10 ng/ml has been used to advise men on the safety of AS regardless of prostate size, the PSAD range in men with a larger prostate was smaller. This may limit the generalizability of our results to men with a large prostate. In addition, as with other AS cohorts, ours is an observational cohort and can only be compared to men who undergo immediate treatment using historical external comparison groups.

CONCLUSIONS

The incidence of significant PCa related events remained low in a cohort with followup beyond 5 years. Additional followup is needed to assess long-term outcomes. Independent of absolute PSA, increased PSAD is a strong marker of future BxR and active treatment. It should be considered along with Gleason score, tumor volume and other disease characteristics when counseling a man on AS.

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