Review Article

Biomarkers in active surveillance

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Abstract: The use of active surveillance (AS) is increasing for favorable-risk prostate cancer. However, there remain challenges in patient selection for AS, due to the limitations of current clinical staging. In addition, monitoring protocols relying on serial biopsies is invasive and presents risks such as infection. For these reasons, there is substantial interest in identifying markers that can be used to improve AS selection and monitoring. In this article, we review the evidence on serum, urine and tissue markers in AS.

Keywords: Prostate cancer; active surveillance (AS); biomarkers; markers

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Introduction

Multiple guidelines now recommend active surveillance (AS) as the preferred approach for management of low-risk prostate cancer (1,2). Randomized trials have shown no difference in the risk of prostate cancer mortality between conservative management and radical treatment in these patients (3). Deferring initial therapy has the further advantage of allowing patients to preserve quality of life for additional years. However, uptake of AS has been highly variable (4), and it remains underutilized in the United States, due to multiple barriers at both the patient and physician level (5). One of the challenges is optimizing patient selection for AS, given the substantial heterogeneity within clinical risk categories and known risk of misclassification. Several markers are now available that can be used to refine risk classification and help with the initial decision to pursue AS.

Monitoring patients during AS remain another major challenge in contemporary practice. Changes in the total PSA level are not reliable predictors of underlying changes in biopsy features during the initial phase of AS (6). However, AS strategies that rely on frequent serial prostate biopsy are associated with added patient burden and risk of side effects. Of particular concern is the increase in infectious complications after biopsy, corresponding with a rising prevalence of antimicrobial resistance in the community (7). Several alternatives are available which have been associated with a lower risk of infection following prostate biopsy, such as use of targeted prophylaxis or using a transperineal approach (8). Nevertheless, biopsy remains an invasive and painful procedure, as well as a source of non-compliance for patients. This creates a need for other non-invasive markers that can be used to help with monitoring of patients during AS. The purpose of this article is to review the markers that can be used for selection and monitoring during AS.

Serum markers

Several studies have examined PSA kinetics during AS using biopsy endpoints, with primarily negative results. In the Johns Hopkins AS program, our group examined the relationship between PSA kinetics with the results of surveillance biopsy during a median follow-up of 2.9 years (6). PSADT was not significantly associated with adverse biopsy findings (P=0.83), and PSAV had a nonsignificant trend (P=0.06). Similar findings were reported in the Royal Marsden program, in which PSAV was significantly

associated with histologic progression on univariable analysis but was not significant in the multivariable model (P=0.069) (9). At UCSF, a PSA doubling time within 3 years was not significantly associated with biopsy progression (OR, 1.4; 95% CI, 0.6–3.4, P=0.46) (10). By contrast, in 120 men from Beth Israel they found that a PSAV >0.11 between the diagnostic biopsy and first rebiopsy was a significant independent predictor of reclassification. The authors created a risk score using PSAV along with family history and PSA density to further stratify the likelihood of biopsy reclassification (11). Notably, more recent studies have shown that PSA kinetics may be more useful for men who have already been stable on AS for several years. For example, Patel *et al.* reported that PSAV risk count (number of occasions that PSAV exceeded a threshold of 0.4 ng/mL/year) was a significant predictor of reclassification among men on AS for at least 2 years (12). Many programs currently use PSA kinetics as an indicator for further diagnostic testing such as MRI or biopsy, rather than as an independent trigger for intervention.

PSA density is another PSA-based parameter which has been studied extensively in AS, and is employed by several AS programs to determine upfront eligibility (13). This is based on studies showing that PSAD >0.15 is associated with an increased risk of biopsy reclassification and receipt of secondary treatment (11,14,15). In the Prostate Cancer Research International: Active Surveillance (PRIAS) cohort, a PSAD <0.2 is one of the inclusion criteria for AS, while Johns Hopkins uses a lower threshold of PSAD <0.15 (13,16). Reese *et al.* reported on men treated by prostatectomy who met some but not all of the Hopkins AS eligibility criteria (17). Overall, 1,205 (14.6%) of the sample were excluded due to a PSAD between 0.15 and 0.2, demonstrating that using a higher PSAD threshold would increase the number of men eligible for AS. However, they reported that men with a PSAD 0.15–0.18 had a significantly higher risk of adverse features at prostatectomy compared to men with a PSAD <0.15.

Alternatively, the percent free PSA (%fPSA) can be used along with the maximum percentage of core involvement to predict the results of the first surveillance re-biopsy and confirm eligibility for AS (18). Two new PSA-based blood tests incorporating free PSA are the Prostate Health Index (phi) and 4K score. Studies from the US and Asia have shown that baseline phi values predict reclassification at 1 year (19,20). Longitudinal values of phi were also shown to predict progression during the course of AS (C-index 0.82). Although not yet studied in the setting of AS, phi density has demonstrated very good predictive value in the diagnostic setting and therefore could prove useful in AS (21). In the Canary Prostate Active Surveillance Study (PASS), the 4K score at diagnosis was shown to improve accuracy for predicting reclassification at the first re-biopsy but not at subsequent AS biopsies (22).

Urinary markers

Several urinary markers have also been explored for use in prostate cancer detection and management. Data are limited in the realm of AS, but some groups have studied the cancer-specific messenger RNA known as prostate cancer antigen 3 (PCA3) and the TMPRSS2: *ERG* gene fusion.

In the setting of AS, PCA3 was initially explored in 294 men at Johns Hopkins with very low risk disease. Urinary PCA3 was measured at a median of 2.5 years following diagnosis, and patients were followed with yearly biopsy for a median of 3.7 years to determine reclassification. The data revealed an association between PCA3 and subsequent biopsy reclassification that did not meet conventional levels of statistical significance (mean value 50.8 and 60.0 in non-reclassified and reclassified, respectively; P=0.131) (23). More recently, these authors performed a longitudinal analysis among AS patients with multiple PCA3 measures obtained over ≥3 years of monitoring (24). Over median 6 years of follow-up, 28 (11%) of 260 eligible men underwent grade reclassification. Men who underwent grade reclassification had a higher initial PCA3 (median 48.0 *vs.* 24.5, P=0.007) and subsequent PCA3 (median 63.5 *vs.* 36.0, P=0.002) than those who did not. Interestingly, the longitudinal change in PCA3 over time did not discriminate those who did and did not undergo grade reclassification (log-normalized rate 0.07 *vs.* 0.06, P=0.53). Overall, these findings suggest that a single PCA3 level can help to predict pathological upgrading during AS, but obtaining multiple measurements over time does not appear to offer additional information.

The multi-institutional Canary PASS investigated both PCA3 and TMPRSS2:ERG in 387 men who were monitored with biopsy at 6 to 12 months from diagnosis, again at 24 months, and subsequently every 2 years (25). The authors observed a significant difference in PCA3 score based on follow-up biopsy results. Median PCA3 scores were 27 in men with a negative biopsy, 31 in those with Gleason score ≤6 disease, and 48 in those with Gleason score ≥7 (P=0.02). Median values of TMPRSS2:ERG were 5, 14, and 29, respectively (P=0.001).

On ROC analysis for prediction of Gleason ≥7 disease, the addition of these markers to PSA had an AUC of 0.70 versus 0.68 for PSA alone (P=0.08).

More recently, Fradet and colleagues explored the use of PCA3 in a unique cohort of AS patients with low-risk prostate cancer who were being treated with a 5-alpha reductase inhibitor (5-ARI) (26). All men were treated with a 5-ARI for at least 6 months (mean, 14.6 months; SD, 10) prior to urine specimen obtainment, which occurred after diagnosis but prior to the initial repeat biopsy. Over a mean follow-up of 45.6 months, 36 (40%) of 90 men underwent grade reclassification to Gleason score ≥7. Adjusting for age, prostate volume, and PSA, a PCA3 score ≥35 was associated with a nearly four-fold increased hazard of grade reclassification (HR, 3.82; 95% CI, 1.91–7.62). A significant relationship was also demonstrated when PCA3 was modeled as a continuous variable (HR, 1.13; 95% CI, 1.01–1.26; P=0.028).

Finally, Zhao *et al.* analyzed DNA methylation patterns of urinary sediment among 153 men with Gleason score 6 cancer monitored on AS (27). The authors considered eight candidate genes for which hypermethylation in radical prostatectomy specimens was associated with high grade cancer and adverse clinical outcomes. Over a median follow-up of 38 (range, 12–44) months, 34 (22%) men were reclassified based on either Gleason score upgrading (n=23), PSADT <3 years, or detecting a PI-RADS 4-5 lesion on MRI. Based on backward logistic regression, a four gene panel (*APC*, *CRIP3*, *GSTP1*, *HOXD8*) was associated with Gleason score upgrading during follow-up (OR, 2.927; 95% CI, 1.264–6.779; P=0.012). Validation in independent cohorts could better establish the utility of these and other urinary markers in the AS setting.

Tissue markers

Multiple tissue based markers are commercially available including the Oncotype DX Genomic Prostate Score (GPS) (28), Prolaris Cell Cycle Progression (CCP) score (29), GenomeDx Decipher score (30), and immunohistochemical (IHC) staining for inactivation of the *PTEN* gene (31). There is a growing body of evidence that tissue-based molecular testing provides prognostic information independent of clinical factors and may aid in decision-making after localized therapy (32,33). Given the utility of these tests in predicting outcomes after treatment, questions have emerged as to whether they could prove useful in selection and monitoring during AS. Unfortunately, these tests have not been well-studied in a true AS population.

We have previously summarized the biologic basis of these tools and reviewed the evidence of their utility in risk stratification (34). Interim data specific to the AS setting have been sparse. In fact, recent reports of the genomic panels have been limited to demonstrating either clinical utility in decision-making (35), or incremental prognostic value among AS-eligible men who were managed definitively (36).

On the other hand, Lokman and colleagues retrospectively assessed PTEN IHC in 190 men managed in PRIAS (37). Tissue from the initial diagnostic biopsies demonstrated PTEN loss in 29 patients (15%). Median cohort follow-up was 46.2 months, during which patients underwent between one and six surveillance biopsies. During follow-up, 106 men (52%) discontinued AS. Seventy-two men (67.9%) discontinued AS for protocol-based reasons (Grade group >1, >2 positive biopsy cores, PSA-DT <3 years, or clinical stage >T2) and 34 (32.1%) for other reasons. In multivariable Cox models, PTEN loss in the diagnostic biopsy was significantly associated with all measured outcomes, including grade group upgrading on rebiopsy (HR, 2.57; 95% CI, 1.16–5.70; P=0.02), treatment change (HR, 2.31; 95% CI, 1.26–4.19; P=0.006), and adverse pathology in men who underwent prostatectomy (HR, 4.75; 95% CI, 1.84–12.23; P=0.001). The number of positive biopsy cores at diagnosis and number of rebiopsy sessions during follow-up were also associated with the study outcomes. These data suggest that the previously observed relationship of PTEN loss with adverse prostate cancer outcomes is consistent in the setting of AS.

Future directions

Very few markers have longitudinal results available among men being monitored during AS, so this is an important area for future research. Once more data become available on the use of markers through the course of AS, we must then determine how to integrate this information with other longitudinal data including the results of serial biopsies. Numerous nomograms are available in the screening context including new markers along with traditional risk factors to predict the risk of aggressive prostate cancer on biopsy. A few groups have recently designed nomograms to predict biopsy reclassification during AS, including the Canary Prostate Active Surveillance Study (including PSA along with clinico-pathologic features) (38) and Johns Hopkins (which includes PSA density along with other clinico-pathologic variables) (39). In the future as

more data accrue, these AS calculators should be updated to incorporate new markers and imaging variables to facilitate the incorporation of multiple factors for clinical decision-making. In the future, customized decision support tools incorporating longitudinal patient data may facilitate a shift from protocol-based to more personalized AS monitoring (40).

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Footnote

Conflicts of Interest: S Loeb received honoraria for lectures from Astellas, MDxHealth and Boehringer Ingelheim, reimbursed travel from Sanofi and Astellas, and consulting for GE, GenomeDx Biosciences and Lilly (unrelated to the current manuscript). JJ Tosoian has no conflicts of interest to declare.

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