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Review Article

Active surveillance in men with low-risk prostate cancer: current and future challenges

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Abstract: Introduction: The implementation of prostate-specific antigen (PSA) screening has coincided with a decrease in mortality rate from prostate cancer at the cost of overtreatment. Active surveillance has thus emerged to address the concern for over-treatment in men with low-risk prostate cancer. Methods: A contemporary review of literature with respect to low-risk prostate cancer and active surveillance was conducted. The premise of active surveillance, ideal candidates, follow-up practices, treatment triggers, and the observed outcomes of delayed interventions are reviewed. Various institutional protocols are compared and contrasted. Results: Eligibility criteria from various institutions share similar principles. Candidates are followed with PSA kinetics and/or repeat biopsies to identify those who require intervention. Various triggers for intervention have been recognized achieving overall and cancer-specific survival rates > 90% in most protocols. New biomarkers, imaging modalities and genetic tests are also currently being investigated to enhance the efficacy of active surveillance programs. Conclusion: Active surveillance has been shown to be safe and effective in managing men with low-risk prostate cancer. Although as high as 30% of men on surveillance will eventually need intervention, survival rates with delayed intervention remain reassuring. Long-term studies are needed for further validation of current active surveillance protocols.

Keywords: Prostate cancer, active surveillance, low risk prostate cancer, active surveillance guidelines

Introduction

Since the introduction of the prostate-specific antigen (PSA) screening in the 1980's, an increase in the incidence of prostate cancer (PCa) has been observed. The initial wave of detection and treatment has led to stage migration. The majority of the newly diagnosed cases are now low-grade and limited volume cancers [1]. In the past, approximately 90% of these cases were treated with definitive therapy with curative intent, i.e. radical prostatectomy (RP) or radiation therapy [2]. Despite a 40% reduction in PCa death since the start of PSA screening era, concerns for over-diagnosis and over-treatment began to emerge [3]. A 2009 randomized European study reported a 20% reduction in mortality in PSA-screened cohort yet highlighting the number needed to treat (NNT) of 48 [4]. Simultaneously, the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial failed to demonstrate statistically significant change in cancer-specific survival between the screened and the control group [5]. Although the conclusions of the PLCO study were biased by a large percentage of contamination within the control group, in 2012 the U.S. Preventive Services Task Force (USPSTF) recommended against routine PSA screening for PCa [6].

The clinical recommendations on PSA screening remain open to debate. However, it is clear that the long-term survival is considerably diminished in men diagnosed with advanced disease. As evidenced in ERSPC study, it is the younger men who may derive the most benefit with an early diagnosis and treatment [4]. The American Urological Association (AUA) has thereby recommended obtaining a baseline PSA at age 40 on its best practice statement [7]. With conflicting data and recommendations, it is often difficult for clinicians and patients to determine the optimal management plan for PCa. Nevertheless, it is clear that not all men with newly diagnosed prostate cancer

need definitive treatment. Indeed, the most effective management of PCa requires selective treatment strategy reflecting the disease and patient characteristics.

The overview

Given the concerns for over-diagnosis and over-treatment for PCa, active surveillance (AS) is now considered the treatment of choice in men with low-risk PCa. AS is distinct from previously proposed watchful waiting (WW) in that WW was generally prescribed to men with multiple comorbidities limiting more definitive treatments. These patients were treated with non-curative intent and only when symptoms developed. In contrast, AS "actively" follows the selected patients in efforts to intervene only at disease progression and thereby delaying the treatment-related complications. This treatment strategy may lead to the quality-of-life (QOL) improvements as reported on the recent update of the Scandinavian study assessing the long-term distress of the patients with PCa [8]. This eight-year follow-up study with QOL questionnaires compared the WW group to the radical prostatectomy (RP) group. Results revealed a similar 30-40% rate of distress with QOL symptoms of worry, feeling low, and insomnia in both groups. However, the RP group was further distressed with leakage, impaired erection, and decreased libido. Similarly, Hayes et al. demonstrated that among hypothetical men age 65 years old with low-risk PCa, the quality-adjusted life-years was the highest with AS compared with brachytherapy, intensity-modulated radiotherapy (IMRT), and RP [9]. It is important, however, to note that although AS is associated with higher QOL, AS population still requires psychosocial support as patient anxiety is an independent predictor of receiving definitive treatment in the AS population [10].

AS as a primary treatment option is utilized in only 25-35% of men aged between 65 and 75 [3]. The Surveillance, Epidemiology, and End Results (SEER) data shows a decline in proportion of men under AS from 44% to 34% over a 14-year period [3]. This underutilization of AS is partly due to the general anxiety faced by the physicians and general population given the limited long-term evidence and universally accepted guidelines. This review will focus on the four current challenges of AS: who to include, how to follow, when to treat and what the outcomes are following delayed intervention.

Challenge 1: who to include?

Risk stratification schemes have been developed based on the post-treatment PSA failure rates and its associations with the pretreatment PSA score, biopsy Gleason score, and American Joint Committee on Cancer (AJCC) clinical stage to define the low-risk PCa [11]. While variations on the scheme exist, the general consensus is that the pre-treatment PSA < 10 ng/mL, biopsy Gleason score of 6 or less and clinical stage T1c or T2a are the characteristics of a low-risk PCa. For this low-risk population, the AUA Prostate Cancer clinical guidelines suggest that at a minimum, AS should be discussed as an acceptable initial intervention along with other definitive therapies [12]. Similar recommendations are made in the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines [13, 14]. These recommendations are based on early retrospective studies showing that the 20-year cancer-specific survival rates have been 80-90% for the low-risk population treated conservatively (i.e. no definitive therapy) [15, 16]. The goal of AS is to identify and monitor this low-risk group and to intervene when necessary. Despite its indolent nature, low-risk PCa can develop local progression and distant metastasis as late as 25 years after diagnosis [17].

This low-risk scheme is further refined to develop the eligibility criteria for AS (**Table 1**). These criteria are based on the pioneering work of Epstein et al. and the others who have attempted to predict clinically insignificant PCa with accuracy ranging between 70-90% [18-20]. The number of positive biopsy cores and percent of cancer in biopsy cores have been shown to be independent predictors of extracapsular extension and pathologic stage after RP [21, 22]. Moreover, PSA density (PSAD) is often included in the risk stratification after Epstein at al. demonstrated that PSAD < 0.1 ng/mL/cm^3 predicted indolent cancer in RP specimen [18]. Dall'Era et al. also reported that PSAD > 0.15 ng/mL/cm^3 can serve as an independent predictor for undergoing intervention [23]. However, it remains unclear whether this is due to the actual difference in tumor biology or increased sampling error with larger gland.

Table 1. Institutional Active Surveillance Protocols

Institutional Protocols	Cohort Size	Mean Follow-up (months)	Eligibility Criteria	Follow-up Methods	Disease Progression	Predictors	% Intervention	OS (%)	CSS (%)
Johns Hopkins [46]	769	32	• ≤ Clinical T1c • PSAD < 0.15 ng/mL^2 • GS ≤ 6 • # of Positive cores ≤ 2 • ≤ 50% cancer involvement of any core	• PSA/DRE every 6 months • Biopsy yearly	• GS > 6 • # of Positive cores > 2 • > 50% cancer involvement of any core	n/a	33.2% at a median of 26 months (26% treated for personal choice without disease progression)	98	100
UCSF [23]	321	43	• ≤ Clinical T1/T2a • PSA < 10 • GS ≤ 6 without grade 4 or 5 • cancer involvement < 33% of biopsy cores	• PSA/DRE every 3 months • Biopsy every 6-12 months (starting 2003, repeat biopsies at 12-24 months)	• Increase in Gleason grade on rebiopsy • Increase in PSAV of > 0.75 ng/mL/year • PSADT < 2 years	• Initial PSAD ≥ 0.15 ng/mL^2 • Increase in Gleason grade on rebiopsy	24% at a median of 36 months after diagnosis (33% treated for personal choice without disease progression)	100	100
Univ. of Miami [51]	230	44	• PSA ≤ 10 • GS ≤ 6 • # of Positive cores ≤ 2 • ≤ 20% cancer involvement of any core	• PSA/DRE every 3-4 months for 2 years then every 6 months • Biopsy in 9-12 months then yearly	• Gleason grade > 3 on rebiopsy • Increase in positive number of cores • Increase in % of tumor in each core	• Any tumor at the first rebiopsy	14% in a mean follow-up of 33 months	100	100
Univ. of Toronto [26]	450	82	• PSA ≤ 10 • GS ≤ 6 • (initially included PSA ≤ 15 and GS 3+4 on men age ≥ 70 up until Jan, 2000)	• PSA every 3 months for 2 years then every 6 months • Biopsy in 6-12 months then every 3-4 years until age 80	• PSADT < 3 years (initially used PSADT < 2 years up until 1999) • Increase in Gleason grade on rebiopsy • Clinical progression	• PSAD • Gleason score at baseline > 6 • Clinical stage at baseline > T2a	30% overall (58% of men in the initial intermediate-risk group were treated)	79	97.2
MSK [52, 53]	238	22	• ≤ Clinical T2a • PSA < 10 • GS ≤ 6 without grade 4 or 5 • # of Positive core ≤ 2 • ≤ 50% cancer involvement of any core	• PSA/DRE every 6 months • Biopsy in 12-18 months then every 2-3 years	• When eligibility criteria was no longer met	• Any tumor at the first rebiopsy	n/a	n/a	n/a
Royal Marsden [50]	326	22	• ≤ Clinical T2a • PSA ≤ 15 • GS ≤ 7 with primary grade ≤ 3 • ≤ 50% cancer involvement of any core	• PSA monthly for year 1 then every 3 months in year 2 then every 6 months • DRE every 3 months for 2 years then every 6 months • Biopsy at 18-24 months then every 2 years	• PSAV > 1 ng/mL/year • Primary Gleason grade ≥ 4 • % Positive biopsy core > 50%	• Free-to-total PSA ratio • Clinical stage	20%	98	100
PRIAS [54]	2494	19	• ≤ Clinical T2 • PSA ≤ 10 • GS ≤ 6 • PSAD < 0.2 ng/mL^2 • # of Positive cores ≤ 2	• PSA every 3 months for 2 years then every 6 months • Biopsy at year 1,4 and 7 • Yearly biopsies if PSADT between 3-10 years	• GS > 6 • PSADT < 3 years after at least 1 year of follow-up • ≥ 3 positive biopsy cores	• PSAD • Number of positive cores (2 vs. 1)	21%	97	100
NCCN [64]	n/a	n/a	• ≤ Clinical T1c (T2a with < 10 yr life-expectancy) • PSA < 10 • GS ≤ 6 • PSAD < 0.15 ng/mL^2 • # of positive cores ≤ 2 • ≤ 50% cancer involvement of any core	• PSA every 6 months • DRE every 12 months • Biopsy as often as every 12 months	• Gleason grade > 3 • Increase in positive number of cores • Increase in % of tumor in each core	n/a	n/a	n/a	n/a

UCSF=Univ. of California–San Francisco, MSK=Memorial Sloan-Kettering, PRIAS=Prostate Cancer Research International: Active Surveillance, NCCN=National Comprehensive Cancer Network, PSA=prostate-specific antigen, GS=Gleason score, PSAD=prostate-specific antigen density, DRE=digital rectal exam, PSADT=prostate-specific antigen doubling time, PSAV=prostate-specific antigen velocity, OS=Overall Survival, CSS=Cancer-Specific Survival.

With some variations, above factors are incorporated in the various AS eligibility criteria (**Table 1**). Iremashvili et al. performed a head-to-head comparison of the Johns Hopkins, University of California-San Francisco (UCSF), University of Miami (UM), Memorial Sloan-Kettering (MSK), and Prostate Cancer Research International: Active Surveillance (PRIAS) criteria [24]. Three-hundred ninety-one patients who had undergone RP with pre-treatment Gleason Score ≤ 6 on transrectal biopsy with ≥ 10 cores were identified. Johns Hopkins protocol was shown to be the most stringent criteria with low sensitivity and high specificity for identifying low-risk PCa on surgical specimen. UCSF and MSK criteria were the most inclusive criteria with the most number of patients, yet included more men with more significant PCa. UM and PRIAS were shown to be more balanced. They included twice as many men as the more conservative protocol, yet showed similar pathologic characteristics of the disease. All five criteria inevitably selected some patients with pathologically more significant disease. Indeed the risk of advanced disease (Gleason score > 6 or non-organ confined disease) is approximately 30-40% in these men with clinically low-risk PCa [25]. Nonetheless, the clinical implications of these aggressive pathologic features in the context of AS is not immediately clear.

In addition to these commonly used AS inclusion criteria, Gleason Score 3+4 intermediate-risk PCa has also been suggested to be reasonable for AS. Klotz at el. from the University of Toronto showed that among men with intermediate-risk PCa only one patient out of 85 patients had experienced progression to metastatic disease and death [26]. Their inclusion protocol, however, eventually excluded men with Gleason Score 3+4 due to the concerns that Gleason Score 7 PCa may behave differently from Gleason Score ≤ 6 PCa [26, 27]. Similarly, we have recently suggested that in men with Gleason score 3+4 PCa, AS may be a viable option if PSA is less than 4.73 ng/mL and % maximum core is less than 15% [28]. Therefore, it is likely that there is a subgroup of men with Gleason 3+4 PCa who are at low-risk for progression. However, additional progress in genomics and proteomics are likely necessary to identify this group.

Given the current status of numerous AS guidelines with no uniformly accepted standard, further research is needed to reach a consensus on the AS inclusion criteria. Considering the indolent nature of low-risk PCa, an ideal inclusion criteria might incorporate the most men initially and later delineate whom to treat based on the evidence of disease progression. To this end, advances in MRI as well as various genetic tests and biomarkers are eagerly anticipated.

Challenge 2: how to follow?

Disease progression is followed with strict protocols under each AS program. Similar to the inclusion criteria, the surveillance protocols from different institutions are variations of common principles (**Table 1**). One of these principles combines serial PSA measurements and digital rectal exam (DRE). Fluctuations in PSA levels may generate anxiety and uncertainty in both patients and physicians as this may indicate disease progression requiring intervention. Not uncommonly, however, it is also a mere biological variation. The concept of PSA kinetics has thus evolved. PSA doubling time (PSADT) has been shown to be significantly shorter in the men who have disease upgrade in their follow-up prostate biopsy [29]. Studies have also identified pre-treatment PSADT as a strong predictor for both biochemical recurrence after radical treatment and cancer-specific survival, suggesting its association with more aggressive forms of PCa [30-32].

Another common principle is the utilization of repeat biopsy. Various studies have already shown relatively high rate of upstaging/upgrading following repeat biopsy [33, 34]. Indeed, most of the disease progressions under AS usually occur within 2 years of starting AS. Berglund et al. noted a 27% upgrade following a 3-month confirmatory biopsy in men eligible for AS [34]. Considering the biology of PCa, this observation is likely due to initial sampling error rather than actual progression of disease. Similarly, Porten at al. demonstrated that a negative repeat biopsy was associated with low risk of progression at 10 years, emphasizing the significance of repeat biopsy in AS protocol [35].

The anatomic location of PCa in the framework of AS has also been examined. Recent studies with 6-8% rate of upgrade in men who have undergone RP either immediately or after period of AS, illustrate that the anterior and transi-

tion zones are most commonly under-sampled on biopsy [36, 37]. Therefore, extended biopsies that target these areas may be warranted to decrease the risk of under-staging in men considering AS [38]. However, the risk of complications with prostate biopsy such as infection, sepsis, lower urinary tract symptoms (LUTS), and erectile dysfunction (ED) cannot be neglected. Fujita et al. noted that while LUTS can be transient, ED may be a long-term complication after repeated biopsies in men with low-risk PCa [39].

Recent challenges to the predictive validity of PSADT [40] and the risk of under-sampling during biopsy have emerged. These modalities may be less ideal as the sole means of following the AS population. Additionally, assessment of prostate biopsy grading especially in low-volume disease is not always consistent even among expert pathologists [41]. Thus, these parameters should be used in combination with other emerging modalities to guide the clinical management.

Magnetic Resonance Imaging (MRI) has recently emerged as an adjunct tool in assessing PCa. Although the conventional T1/T2-weighted MRI lacks adequate accuracy in staging early PCa [42], multiparametric MRI (MP-MRI) has demonstrated usefulness in AS. Mullins et al. reported that in their cohort of 50 men, MP-MRI demonstrated specificity and negative predictive value of 0.97 and 0.89 respectively for detection of significant cancer with biopsy [43]. This suggests a lack of suspicion on MRI is highly predictive of negative biopsy results. Suspicious MP-MRI results have also been associated with reclassification, i.e. not meeting AS criteria on repeat biopsy results [44]. Moreover, Wang et al. demonstrated that the preoperative endorectal MRI (eMRI) imaging is significantly associated with seminal vesicle invasion on RP pathology specimens [45]. Taken together, these studies propose the potential utility of MRI in the AS surveillance regimens. Although a standardized protocol does not yet exist, most institutions have incorporated the above findings to detect disease progression and to adequately select those in need for intervention. Perhaps, addition of new biomarkers may help improve the outcome of AS during the follow-up period.

Challenge 3 and 4: when to treat and what the outcomes are following delayed intervention?

The triggers for intervention in patients on AS vary across the literature. Different guidelines incorporate a varying combination of changes in DRE, PSA kinetics, clinical stage, grade and volume. The correlation between rapid rise in pretreatment PSA and the associated death related to prostate cancer is well recognized [31]. PSA velocity greater than 0.75 ng/mL/year and PSADT of less than 2 to 3 years are often advocated as a cutoff for recommending treatment [23, 26, 46-48]. However, conflicting data exists that questions the role of post-diagnostic PSA kinetics in predicting adverse pathology [40]. Thus, the PSA kinetics have been recently challenged due to its potential for leading to overtreatment in men on AS [48, 49]. On the other hand, progression on biopsy pathology remains an absolute trigger for intervention in many AS protocols (**Table 1**). Differences in defining pathologic progression on biopsy results such as changes in Gleason score as oppose to changes in any number of positive core or percent cancer in any core still exist among these institutions.

Klotz et al. described that out of 450 patients enrolled in the Toronto AS program, definitive therapy was offered to 30% of the patients with an unequivocal clinical progression as demonstrated by PSADT of < 3 years or histologic upgrading to Gleason score ≥ 4+3 [26]. Out of 117 patients who received treatment, the PSA failure rate was 50%. Nevertheless, after median follow-up of 6.8 years, cancer specific survival was 97.2% and overall survival was 78.6%. Additionally, authors noted PSADT < 3 years was associated with 8.5-fold higher risk of biochemical failure following treatment. Therefore, it could serve as a reliable marker for aggressive disease. The PRIAS study, one of the largest series on AS with 2492 men with mean follow-up of 19 months, reports the number of positive cores and PSAD to be the strongest predictors for reclassification and intervention. Additionally, PSA velocity > 1 ng/mL/year was used as a trigger to treat by Van As et al. in their AS experience with 326 men at Royal Marsden [50]. The free-to-total PSA ratio was associated with time to intervention in their study.

The series by Tosoian et al. describing the more stringent Johns Hopkins experience of the 769

Table 2. Rutgers-CINJ Active Surveillance Protocol

Inclusion Criteria	Follow-up Methods	Disease Progression
• PSA < 10	• Pelvic MRI at diagnosis	• Increased Gleason score
• Gleason score ≤ 6 without grade 4 or 5	• Confirmatory biopsy in 3-6 months	• Increase in number of positive cores
• Clinical stage ≤ T2a	• Repeat biopsies at year 1, 3, and 5 after confirmatory biopsy	• PSADT < 3 years
• ≤ 3 positive cores	• PSA every 3 months for year 1, then every 6 months thereafter	• If pelvic MRI is positive
• ≤ 50% cancer involvement in any core	• Pelvic MRI at year 1, 3, and 5 immediately prior to biopsy. If positive, intervention without further diagnostic tests.	

PSA=prostate-specific antigen, GS=Gleason score, PSADT=prostate-specific antigen doubling time, MRI=magnetic resonance imaging.

men, showed that 255 (33.2%) men underwent treatment following median of 2.2 years on AS. Curative therapy was recommended if surveillance biopsy demonstrated disease upgrade to Gleason score > 6 or > 2 positive cores with cancer or > 50% cancer involvement of any core [46]. After a median follow-up of 32 months, the 10-year cancer specific survival was noted to be 100% with the overall survival of 98.2%. Similarly, Soloway et al., in their update of AS experience in 2010, found neither PSADT nor clinical stage to be predictors of treatment [51]. In their cohort, reasons for intervention included Gleason upgrade, increase in tumor volume or > 2 positive biopsy cores. Out of 230 patients on AS, 32 (14%) received treatment with median follow-up of 44 months. Twelve of these patients underwent total prostatectomy and none of these patients had experienced biochemical recurrence. At MSK, progression is defined as patient no longer meeting eligibility criteria, i.e. PSA ≥ 10 ng/mL, Gleason score upgrade to ≥ 7, ≥ 3 positive cores and > 50% cancer in any core [52, 53]. After median follow-up of 1.8 years, 61 out of 238 men on AS experienced disease progression. The progression-free probability at 2 and 5 years was 80% and 60% respectively. Excluding the patients who progressed only on the basis of PSA rise, only 32 cases progressed and the progression-free probability at 2 and 5 years was 91% and 76% respectively. Positive confirmatory biopsy was the only independent predictor of progression using this modified criteria. Based on these results, the authors conclude there is little justification for treatment decision based solely on PSA rise > 10 ng/ml in the absence of other indications of tumor progression.

Dall'Era et al. reported the UCSF experience in 321 men. The triggers for intervention included histologic progression and changes in PSA velocity (> 0.75 ng/mL/year) [23]. Twenty-four % of patients were treated after a median of 3 years on AS. Both the 10-year overall survival and cancer specific survival were 100%. Interestingly, the authors noted that select patients with low-volume Gleason 3+4 cancers, especially those with competing comorbidities may be suitable for AS. At 4 years, the progression free survival for low-risk group (54%) was comparable to intermediate-risk group (61%) (p=0.22) [47]. Neither group was noted to have nodal disease at the time of surgery or biochemical recurrence within 3 years. Along with earlier results with intermediate-risk PCa group by Klotz et al. [26], this study suggests prospect of AS for carefully selected intermediate-risk men. The efficacy and safety of such protocol still needs to be confirmed.

Majority of the above protocols have reported overall survival and cancer-specific survivals of > 90% with the largest PRIAS cohort showing the 2-year overall survival of 97% with the prostate cancer-specific survival and the calculated 10-year overall survival of 100% and 77% respectively [54]. Van den Bergh et al. also demonstrated that there were no differences in biochemical recurrence-free survival after immediate or delayed surgery in men eligible for surveillance [55]. Furthermore, aggregate data from published surveillance cohorts have demonstrated that the PCa specific survival was greater than 99% at a median follow-up of 43 months. Taken together, these studies provide support towards AS programs for subset of patients with low volume and low risk PCa. Longer follow-up data is pending to further assess the long-term efficacy and safety of current AS protocols.

Our experience

Our AS experience at the Rutgers-Cancer Institute of New Jersey (Rutgers-CINJ) is also aimed at tailoring the optimal protocol for AS (**Table 2**). Our inclusion criteria is PSA < 10,

Gleason score ≤ 6, clinical stage ≤ T2a, ≤ 3 positive cores with ≤ 50% cancer involvement in any core. Our patients are followed with pelvic MRI at diagnosis, confirmatory biopsy in 3 to 6 months with repeat biopsies at year 1, 3 and every 2 to 4 years thereafter. Additionally, PSA is obtained every 3 months for the first year then every 6 months thereafter. We also perform pelvic MRI at year 1, 3 and 5 immediately prior to biopsy to offer intervention without additional diagnostic tests if pelvic MRI is positive. Our triggers for intervention include Gleason score upgrade, increase in number of positive cores on repeat biopsy and PSADT < 3 years. Detailed results of the Rutgers-CINJ AS protocol from more than 150 men will be available in the near future.

The future

Over the last decade, there have been significant advances in the biology of PCa. New biomarkers are being investigated and new modalities are being developed to help distinguish indolent cancer from more aggressive forms. The Prostate Active Surveillance Study (PASS), a multicenter study sponsored by National Institutes of Health (NIH), is currently investigating biospecimens (blood, urine and prostate tissue) in search of the novel biomarkers in detection and surveillance of PCa [56]. One of the most studied biomarkers is Prostate Cancer Antigen 3 (PCA3), a non-coding gene specific to prostate that is overexpressed in PCa. Though still controversial, one study has demonstrated the urine PCA3 to be superior to PSA in predicting repeat-biopsy outcome in men with elevated PSA with negative initial biopsy [57]. These novel biomarkers may be a valuable tool in counseling men considering AS.

As mentioned earlier, MRI imaging has a role in detecting disease progression. A study with 114 men with median follow-up of 59 months showed a four-fold increase in Gleason upgrading at subsequent biopsy if suspicious lesion was seen on MRI [58]. Lee et al. also described that non-visualization of tumor on MP-MRI was an independent predictor of organ-confined, Gleason score 6 disease after RP [59]. The high negative predictive value of MP-MRI ranging at 89-98% in excluding high grade tumor supports MRI as a surveillance tool in men on AS [43, 60].

Multigene assays are currently under investigation with aims to overcome tumor heterogeneity in men with low-risk PCa. Although the exact determinant factors are still not well understood, three risk factors have been identified in development of PCa: increasing age, ethnicity and heredity. Examining genetic influences would help identify men with greater risk. Tumor genetics is already incorporated into the management guideline for breast cancer and is currently being evaluated at as prognostic predictor in colon cancer [61, 62]. Oncotype DX® and Prolaris® are the examples of these multigene assays that are currently available for PCa prognostication. For Oncotype DX®, 17 genes across multiple biological pathways have been identified from the RP and biopsy specimens to generate a genomic prostate score (GPS). Cooperberg et al. reported that GPS from biopsy specimen strongly predicted ($p < 0.005$) high grade and/or pT3 disease in their validation study with 395 men [63]. They also described that GPS could be obtained from as little as 1 mm tumor length in the biopsy specimen. Prolaris® likewise utilizes 46 gene expression signatures to generate a cell cycle progression (CCP) score. CCP score has been shown to be a strong independent predictor of cancer death outcomes [65]. These assays could significantly improve the risk stratification of AS patients and potentially even decrease the sampling errors in prostate biopsies. One potential implementation of such assays includes prognostication of African American (AA) men with low-risk PCa. AA men eligible for AS have been shown to be more likely to have worse pathological features on final surgical pathology as compared to White American men on AS [66]. They are also more likely to have disease upgrading and positive surgical margins at RP [67]. The multigene assays can aid to appropriately select and counsel these men considering AS as the treatment option in near future.

Conclusion

The PSA-era has resulted in an increased diagnosis of PCa with subsequent decreased PCa-specific death. However, this was achieved at the cost of overtreatment. In this regard, AS appears to be a pragmatic treatment option in the management of low-risk PCa. Further studies are needed to develop a universally validated protocol for AS. Likewise, the socioeconomic challenges and psychosocial support must be

addressed to ensure wide dissemination of AS. New biomarkers, imaging studies, and genetics will likely enhance the efficacy of AS in the future.

Disclosure of conflict of interest

None.

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