

Review Article

# Divorcing Diagnosis From Treatment: Contemporary Management of Low-Risk Prostate Cancer

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Today, the majority of men with newly diagnosed prostate cancer will present with low-risk features of the disease. Because prostate cancer often takes an insidious course, it is debated whether the majority of these men require radical treatment and the accompanying derangement of quality of life domains imposed by surgery, radiation, and hormonal therapy. Investigators have identified various selection criteria for “insignificant disease,” or that which can be monitored for disease progression while safely delaying radical treatment. In addition to the ideal definition of low risk, a lack of randomized trials comparing the various options for treatment in this group of men poses a great challenge for urologists. Early outcomes from active surveillance cohorts support its use in carefully selected men with low-risk disease features, but frequent monitoring is required. Patient selection and disease monitoring methods will require refinement that will likely be accomplished through the increased use of biomarkers and specialized imaging techniques.

**Keywords:** *Diagnosis; Disease management; Prostate neoplasms*

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## INTRODUCTION

Prostate cancer is the second most frequent cancer diagnosis in men, and the estimated incident cases of the disease worldwide exceeded 900,000 in 2008 [1]. Global incidence varies tremendously, reflecting local and regional genetics, diet and other environmental exposures, socio-demographic characteristics, life expectancy, and screening and diagnostic clinical practices. As in other countries with active screening efforts, in the United States prostate cancer is the most common male cancer diagnosis, with 238,590 new cases and 29,720 deaths estimated to occur in 2013 [2]. The age-adjusted standardized incidence rate varies sevenfold within the United States by region and ethnic group, from a low of 30.9 per 100,000 for Koreans in Los Angeles County to a high of 216.0 among African Americans in and around Detroit. Across Asia, likewise, incidence rates vary tremendously, from 1.4 in the Jiashan region of China to 50.2 in Israel. Among Asians in the United States, the incidence rate 58.0 is higher than any-

where in Asia [3].

The introduction of prostate-specific antigen (PSA) screening in the late 1980s was a pivotal event in the field of urology, as this tool allowed for increased detection and subsequent reductions in prostate cancer mortality [4]. However, widespread use of PSA testing has also contributed to the increased detection of lower risk disease. The contemporary profile of prostate cancer is marked by a rise of nonpalpable T1c tumors, an increased proportion of men with  $\leq 10\%$  of biopsy cores positive, and a declining mean PSA [5]. These tumors may never cause any morbidity or mortality if left untreated, and this “overdiagnosis” is estimated to reflect up to 60% of cases [6,7].

The larger problem is that overdiagnosis leads to overtreatment, with corresponding treatment-related morbidity and declines in quality of life (QoL). Additionally, men with incident prostate cancer are younger [8], and earlier exposure to intervention and the potential for treatment-related bowel, urinary, and sexual toxicity strongly argues for consideration and preservation of QoL domains

until the tumor becomes a threat. Our field lacks consensus in defining the optimal management strategy for those with localized prostate cancer. Increasing evidence on the safety of delayed treatment and the success of active surveillance (AS) for carefully selected patients is fueling the debate against radical treatment in those with presumably indolent disease. The objective of this review was to discuss contemporary treatment strategies in men with low-risk features.

## TO TREAT OR NOT TO TREAT?

In the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, PSA-based screening was associated with a 20% reduction in mortality, provided 1,410 men are screened and 48 are treated in order to prevent 1 prostate cancer death within 9 years [9]. (The Prostate, Lung, Colon, and Ovarian trial, published simultaneously, did not allow conclusions to be drawn regarding screening owing to the extremely high rates of PSA testing in the “control” arm [9,10].) This study highlighted the concern regarding overdiagnosis. Conversely, with a longer follow-up of 14 years, a substantial benefit of screening was observed in the Göteborg trial, which found a 44% reduction in cancer death, with only 293 needing to be screened and 12 treated to prevent 1 prostate cancer death [11].

Although this needed-to-treat number is closer to that seen for other screening-detected tumors, it still means that 11 men will be diagnosed and potentially treated without any benefit to mortality to save one life from prostate cancer. Overdiagnosis is problematic, because in the United States and other developed countries, detection often results in treatment [7,12] and its associated adverse effects, which have fueled criticisms against PSA screening. In fact, the impact of PSA screening on QoL was reported by ERSPC investigators to be tempered by a 23% reduction in QoL years, which was attributed to post-diagnosis long-term effects [13].

AS is a primary management strategy that provides men the alternative of monitoring their cancer, with delayed intervention prompted by tumor progression, thereby avoiding unnecessary treatment and treatment-related morbidity until it is actually required. Several recent trials that have randomized men with low-risk disease to either surveillance or intervention are emerging. Results from the Prostate Cancer Intervention Versus Observation Trial (PIVOT), a large randomized controlled trial, found no benefit in prostate cancer-specific mortality associated with surgery compared with observation for patients with low-risk disease, whereas benefits were substantial in those with higher risk disease [14].

In contrast, data from a randomized, multicenter Scandinavian study found that prostatectomy offered a survival advantage over watchful waiting, even among low-risk men [15]. However, men in this latter study were diagnosed before the PSA era and therefore reflect a population with higher risk disease than is seen in typical AS cohorts

(however, few men in this study had high-grade or otherwise high-risk disease). Furthermore, a watchful waiting approach was taken in which patients were managed expectantly with palliative therapy for those who developed symptoms of advanced disease. This differs from AS in which men are monitored for signs of disease progression with the goal of timely curative intervention. As reports on the relative safety of AS and delayed treatment are emerging [16], the initial question for most men today with low-risk features is no longer what modality of treatment to pursue, but rather when if ever treatment will be required.

## RISK STRATIFICATION

Defining prostate cancer risk, or the risk of progression, recurrence, or metastasis, is critical to informing practitioners and patients about prognosis and the likelihood of response to treatment, which can aid clinical decision making [17]. The traditional three-level risk classification system (low, intermediate, and high risk), which was first described by D'Amico et al. [18] and later endorsed by the National Comprehensive Cancer Center (NCCN), defines “low-risk” disease as clinical stage, T1 to T2a; PSA,  $\leq 10$  ng/mL; and Gleason sum,  $\leq 6$ . Kattan et al. [19] published a preoperative nomogram, subsequently well validated, that was based on similar diagnostic characteristics and that predicts the likelihood of 5-year biochemical-recurrence-free survival after prostatectomy. In 2005, the University of California, San Francisco developed the Cancer of the Prostate Risk Assessment (CAPRA) score to assist in predicting recurrence-free survival. The CAPRA score ranges from 0 to 10 and is determined on the basis of age, preoperative PSA, Gleason sum, clinical T stage, and percentage of positive biopsy cores [20]. These tools are relatively simple and easy to use and have undergone extensive external validation of multiple endpoints including recurrence, metastasis, and mortality [21-25].

The importance of careful substratification of men with low-risk disease was exemplified in a retrospective study of men enrolled within the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry [5]. Investigators reviewed diagnostic features and pathologic outcomes of men designated as NCCN low risk and found that with each 1-point increase in CAPRA score above 0, a corresponding linear decrease in the 5-year actuarial biochemical-recurrence-free survival rate was observed [5]. This finding highlighted that the NCCN “low-risk” category does not discriminate against a primary or secondary Gleason score of 4, because some men with Gleason sum 6 disease could be designated as low risk (Gleason 4+2 or 2+4), but the presence of Gleason pattern 4 clearly predicted worse outcomes. Thus, whereas risk nomograms are essential for predicting treatment outcomes, our current tools have clear limitations. More recently, the overdiagnosis-overtreatment debate prompted the NCCN to define a new risk category termed “very low risk,” referring

to T1c disease; Gleason score,  $\leq 6$ ; PSA,  $< 10$  ng/mL; fewer than 3 biopsy cores positive with  $\leq 50\%$  cancer in each core; and a PSA density,  $< 0.15$  ng/mL/g [17].

Although less common for men with lower risk disease, the rate of biopsy and pathological stage incongruence in one recent study that prospectively reviewed men with low-risk disease (NCCN criteria) and very low risk disease (T1c; PSA density,  $\leq 0.15$  ng/mL; Gleason score,  $\leq 6$ ;  $\leq 2$  positive biopsy cores; and  $\leq 50\%$  involvement of cancer in any single core) found 23.1% and 8.5% of men, respectively, had non-organ-confined disease on surgical pathology [26]. These data are based on the difference between preoperative biopsy and final pathology at the time of radical prostatectomy (RP), which highlights the importance of a second confirmatory biopsy in selecting men who would be candidates for surveillance. Biopsy Gleason sum as well as the number or percentage of biopsy cores with cancer have all been found to independently predict risk of extracapsular extension, as shown in one study of Korean men who underwent prostatectomy for localized prostate cancer [27]. Importantly, no method exists that can predict disease progression or aggressiveness with complete accuracy. Novel technologies, including serum markers and imaging, will allow better risk stratification and prediction of progression to guide clinical decision making.

Currently, literature on AS outcomes is largely limited to United States and European ethnicities. There is an established disparity in incidence and prostate cancer aggressiveness between Western and Asian nations [27], which puts into question the safety and efficacy of AS in these populations. Recent reports from Japanese [28] and South Korean [29] cohorts that identified men with low-risk disease who met the PRIAS (Prostate Cancer Research International: Active Surveillance) criteria (Gleason score,  $\leq 6$ ; T1c-T2; PSA,  $< 10$  ng/mL; PSA density,  $< 0.2$ ;  $< 2$  positive cores) reported similar rates of unfavorable pathologic outcomes as compared with Western studies. Nonetheless, profiles of "insignificant disease" in Asian men appear to be unique [27]; thus, validation of optimal selection criteria is warranted.

## PRIMARY TREATMENT MODALITIES AND DECISION MAKING

The literature comparing primary treatment strategies for men with low-risk disease is relatively sparse, because data are available from only a few observational studies and current prospective trials have yet to be completed. Furthermore, because metastatic disease is rare in men with low-risk disease, absolute differences in survival outcomes between treatments are minimal; thus, differences in QoL outcomes are at least as relevant in guiding treatment decisions. Furthermore, comparison of therapies with clinical endpoints such as PSA or biochemical recurrence is not possible between surgical and radiation modalities owing to differences in the definition of post-treatment recurrence [30,31]. Additionally, because PSA fail-

ure does not uniformly lead to clinical metastasis or death [32], this measure may not be an entirely valid proxy to compare treatments.

Although current North American and European guidelines recommend that patients with low-risk disease be considered for AS [17,33,34], this treatment approach remains relatively underutilized [35]. However, interest in this alternative is rapidly increasing, at least in academic settings. Various AS selection criteria have been reported [36-49], commonly including diagnostic Gleason sum,  $\leq 6$  (no pattern 4 or 5 disease); PSA, 10 ng/mL; and  $\leq T2a$  disease (Table 1). Variable criteria, including PSA density, 0.15; no more than 2 cores positive; and less than 50% of any single core positive, are used as predictors of "insignificant cancer" as defined by low-volume as well as low-grade disease [50].

Delayed treatment occurs in up to a third of men during median follow-up ranging from 1.8 to 6.8 years as described in contemporary series (Table 2) [37,39,41,43,45,47,49]. Studies examining prostate specimens of those with delayed prostatectomy found no difference in pathological or mortality outcomes compared with those who were treated immediately [40,51,52]. The largest driver of treatment is grade progression, including an increase in volume or an upgrade to Gleason 4 disease on repeat biopsy, but PSA kinetics such as doubling time or velocity are commonly used intervention triggers of the monitoring protocols in contemporary series (Table 1). Patient anxiety is also an important potential driver for treatment [53]. Therefore, QoL measures are especially important to consider in primary treatment decision planning.

In a recently published decision analysis of men with low-risk disease, quality-adjusted life expectancy (QALE) was compared between those treated with AS, RP, brachytherapy (BT), or external beam radiation therapy (EBRT) [54]. The study reported that men who underwent AS had the highest QALE. In addition to minimizing treatment-related morbidity, the reportedly very low prostate cancer-specific mortality ( $\leq 3\%$ ) of these AS series makes surveillance very appealing in men with low-risk disease, but most of these data represent relatively short-term follow-up given the long natural history of low-grade prostate cancer. Additionally, monitoring protocols vary substantially between institutions and triggers for intervention have yet to be standardized [55,56].

Efforts to identify better markers of progression will allow us to detect men who are most suitable for AS with less uncertainty regarding their risk of progression and to select out men who are most likely to derive benefit from immediate treatment. Furthermore, additional prospective trials randomizing men between AS and intervention are underway. The ProtecT (Prostate Testing for Cancer and Treatment) study is sponsored by nine centers in the United Kingdom. Between 1999 and 2008, around 2,000 patients were randomly assigned to surgery, radiation therapy, or AS, and biochemical recurrence, clinical progression, and QoL measures are being evaluated [57,58].

**TABLE 1.** AS series selection criteria and monitoring protocols

Institution	Year	Selection criteria	Monitoring protocol
Johns Hopkins	2011 [37] 2008 [36]	T1c; Gleason, $\leq 3+3=6$ ; PSAd, $\leq 0.15$ ; max 2 positive cores	6 Monthly PSA and DRE; annual biopsy
University of Toronto	2010 [39] 2006 [38]	T1c; PSA, $\leq 10-15$ ; Gleason, $\leq 3+3=6$	3 Monthly PSA and 6 monthly DRE for 2 years; 6 monthly PSA and annual DRE thereafter; biopsy 6-12 months first year then every 2-3 years
UCSF	2011 [41] 2008 [40]	T1 or T2a; PSA, $\leq 10$ ; Gleason, $\leq 3+3=6$ ; $<33\%$ positive cores	3 Monthly PSA with DRE and TRUS every 6-12 months; biopsy every 1-2 years
Royal Marsden	2008 [43] 2007 [42]	cT, $\leq 2a$ ; Gleason, $\leq 3+4$ ; PSA, $\leq 15$ ng/mL; $\leq 50\%$ positive biopsy cores	Monthly PSA first year, 3 monthly second year and 6 monthly thereafter; DRE 3 monthly for 2 years then 6 monthly thereafter; initial repeat biopsy at 18-24 months, then every 2 years
University of Miami	2010 [45] 2008 [44]	$\leq 2$ cores positive or $\geq 20\%$ cancer in any core	3-4 Monthly PSA and DRE for 2 years; 6 monthly thereafter; annual biopsy (or earlier for PSA/DRE change)
Memorial Sloan-Kettering Cancer Center	2011 [47] 2004 [46]	cT, $\leq 2a$ ; PSA, $\leq 10$ ng/mL; Gleason, $\leq 3+3$ ; $\leq 3$ positive cores; $\leq 50\%$ single core positive	Semiannual DRE, free and total PSA; initial repeat biopsy 12-18 months of starting AS, then repeated every 2-3 years (or earlier if change in DRE or sustained PSA increase)
Multicenter European study (ERSPC)	2009 [49] 2007 [48]	T1c or T2; PSA, $< 10$ ; Gleason, $\leq 3+3=6$ ; PSAd, $< 0.2$ ; max 2 positive cores	3 Monthly PSA and 6 monthly DRE; biopsy at 1, 2 and 7 years or cT3 or PSA-DT, $\leq 3$ years <sup>a</sup>

AS, active surveillance; PSAd, prostate specific antigen density; PSA, prostate specific antigen; DRE, digital rectal examination; UCSF, University of California San Francisco; TRUS, transrectal ultrasound; ERSPC, European Randomized Study of Screening for Prostate Cancer; PSA-DT, prostate specific antigen doubling time.

<sup>a</sup>:Changed to  $\leq 10$  years recently.

**TABLE 2.** Treatment and oncologic outcomes of active surveillance series

Institution	No. of treated (%)	Primary trigger for treatment	Time to treatment (y), median	10-Year OS	10-Year CSS
Johns Hopkins [31,32]	255 (33)	Grade/volume	2.2	98.2 <sup>a</sup>	100 <sup>a</sup>
University of Toronto [33,34]	135 (30)	PSA	N/A	78.6	97.0
UCSF [35,36]	113 (30)	Grade/volume	3.5	98.0	100
Royal Marsden [37,38]	65 (20)	NA	1.3	98.0 <sup>b</sup>	100 <sup>b</sup>
University of Miami [39,40]	67 (20)	Grade/volume	2.6	100 <sup>a</sup>	100 <sup>a</sup>
Memorial-Sloan Kettering [41,42]	25 (11)	Grade/volume	NA	N/A	N/A
Multicenter European study [43,44]	197 (32)	PSA	2.6	77.0	100

OS, overall survival; CSS, cancer specific survival; PSA, prostate specific antigen; UCSF, University of California San Francisco; NA, not available.

<sup>a</sup>:Provided median follow-up of 32 months. <sup>b</sup>:Provided median follow-up of 22 months.

Unfortunately, poor accrual has led to termination of other prospective trials comparing AS with radical intervention [59].

Other options in the management of men with low-risk tumors include immediate definitive treatment via surgery or radiation. RP is the mainstay primary intervention for men with localized prostate cancer [5]. Furthermore, oncologic outcomes do not appear to be compromised with the use of the relatively new robotic technology [60] that has gained popularity over the open approach [61]. Long-term oncologic outcomes, such as PSA recurrence and cancer-specific survival, are directly influenced by degree of clinical risk and presence of high-risk features [62-64]. Eggenner et al. [65] reported 15-year survival out-

comes of men diagnosed and treated in the PSA era and in a nomogram found that pathologic Gleason score 8-10 disease and seminal vesicle invasion were the primary determinants of cancer-specific mortality after RP. That finding corroborated the suggestion from the PIVOT trial that the benefit of RP was largely in those with higher-risk features.

Zelevsky et al. [66] assessed 8-year freedom from metastatic progression in a cohort of men with localized prostate cancer and found an overall significant improvement in those who underwent primary RP compared with radiation, whereas adjusted absolute differences in metastasis-free survival rates were similar for men with low-risk disease, further highlighting the favorable oncologic features of men with low-risk disease and the need for

aggressive identification and treatment of higher-risk disease. Morbidity from treatment differs by modality, with urinary incontinence and erectile dysfunction comprising the major concerns for men who undergo RP [66-69].

Radiotherapy is another option for men with low-risk prostate cancer and can be offered as either EBRT or permanent interstitial BT. There have been numerous technological advances in EBRT since it was first utilized in the 1930s, with the most recent development being of image-guided precision techniques. Since the 1990s, intensity modulated radiation therapy (IMRT) has further refined treatment delivery. Improved dose localization has allowed for increased doses, which have been shown to improve biochemical outcomes [70-72]. A population-based cohort study using Surveillance, Epidemiology and End Results-Medicare data of men treated with either primary three-dimensional conformal radiation therapy (3D-CRT) or IMRT found that men with low-risk disease treated with IMRT had a similar likelihood of undergoing salvage androgen deprivation therapy (ADT) as well as a similar risk of developing a complication requiring intervention [73]. Permanent interstitial BT may also be appropriate for patients with low-risk disease [17,34], because cancer control rates compare to surgery for these patients [74].

Men with low- or intermediate-risk disease who undergo high- or low-dose BT vs. IMRT had comparable biochemical control and cancer-specific survival, but the cost of IMRT was substantially higher [75]. Side effects following radiation therapy are primarily irritative, involving urinary or bowel symptoms [33], with rates known to increase with higher treatment doses [76] or when BT is combined with EBRT [77]. Both scenarios are less common in low-risk patients. As with surgery, radiation may be associated with a significant impact on sexual health [33,78]. Regarding the role of concurrent ADT, the data largely support that primary or neoadjuvant hormone therapy provides little benefit and may be harmful to men with low-risk disease [79]. In a recent phase three clinical trial that evaluated the addition of short-term ADT to radiotherapy in men with localized disease and PSA < 20, a post hoc risk analysis showed that the benefit was limited only to those classified as intermediate risk, whereas no benefit was seen in the low-risk group [80].

With an absence of randomized trials to guide decisions regarding the treatment of localized prostate cancer, comparative effectiveness studies using observational data are an important addition to the prostate cancer literature. Several of these studies have reported higher cancer-specific survival in men treated with RP than in those treated with radiation therapy, but this effect was largely limited to those with higher risk features [66,81-83]. Kibel et al. [82] in a large, contemporary, comparative analysis compared overall and cancer-specific survival for men with localized disease who underwent either RP, EBRT, or BT. The reported adjusted 10-year overall survival for RP was 88.9%, compared with 82.6% for EBRT and 81.7% for BT.

Additionally, RP offered lower cancer-specific mortality compared with either radiation therapy (1.8% vs. 2.9%, 2.3%). However, for men with low-risk disease, although lower overall survival was observed for both EBRT (hazard ratio, 1.7;  $p < 0.001$ ) and BT (hazard ratio, 1.7;  $p < 0.001$ ) compared to RP, no significant differences were seen in cancer-specific mortality.

In a report from CaPSURE, a large, national community-based registry of men who are followed prospectively, 10-year cancer-specific mortality was twofold higher for EBRT and threefold higher for ADT groups than for the surgery group, with negligible differences noted for low-risk patients [83]. The oncologic superiority of open RP compared to IMRT was also confirmed in a comparative decision analysis, but this finding was, likewise, limited to those with intermediate- and high-risk disease features. Thus, the absence of superiority of these modalities in the control of low-risk prostate cancer suggests that clinicians should strongly consider other factors, such as QoL and cost, in treatment decisions.

QoL measures were compared for men who underwent watchful waiting vs. prostatectomy in the Scandinavian trial described above [84], which included longitudinal data collection from a subset of men. The study found that patients undergoing surgery compared with watchful waiting had a larger prevalence of erectile dysfunction (84% vs. 80%) and urinary leakage (41% vs. 11%). The authors reported that men in the surgical arm reported more distress from these symptoms than did men in the watchful waiting arm. Among men with longitudinal assessment, there was less increase in physical symptoms in the surgical arm (45% vs. 60%) than in the watchful waiting arm but similar rates of reduction in QoL (61% vs. 64%, respectively) [84]. Cooperberg et al. [85] performed a comprehensive, lifetime decision analytic model to follow hypothetical men with low-, intermediate-, and high-risk prostate cancer after primary treatment with either RP or radiation therapy (3D-CRT, IMRT, BT, or combination). Among men with low-risk features, QoL years were slightly greater for those who underwent surgical vs. radiation modalities, and within radiation modalities, 3D-CRT was the least effective. There were no significant differences noted between various surgical modalities.

However, the lifetime cost of prostatectomy was lowest for prostatectomy for low-risk disease (\$20,000). Radiation therapy costs varied considerably by risk and modality type. For men with low-risk features, BT costs are estimated to be \$25,000, whereas IMRT costs \$37,700. These authors emphasize that cost estimates were based on Medicare (government insurance) payment rates and did not include hospital costs [86]. Proton beam therapy has been advocated more recently for prostate cancer, but a clear benefit over IMRT photon therapy has yet to be demonstrated, and the costs are extraordinarily high [87]. There is mounting criticism over the increased use of new, expensive modalities because there is inadequate evidence to confirm superior oncologic efficacy of current treat-

ments, especially in the setting of low-risk disease [87]. In addition to cancer control, treatment-associated costs and morbidity are factors that must be considered in primary treatment decision making.

## LOOKING FORWARD

The future holds promise for the identification of better biomarkers or tools that predict disease progression, which will help clinicians decide which patients will benefit from immediate radical intervention and which patients can pursue AS strategies. Serum or urinary biomarkers are currently under investigation as potential tools to assess clinical risk to assist in treatment decision making. RNA-based urine biomarkers (i.e., prostate cancer antigen 3 [PCA3], TMPRSS2-ERG fusion gene) are the most well-studied class and demonstrate potential clinical utility. Urinary PCA3 is highly overexpressed in prostate tumors [88] and has been investigated as a first-line diagnostic test in prescreened men. PCA3 has been shown to correlate with biopsy outcome [89,90]. In AS cohorts, PCA3 was found to predict disease volume [91,92] and biopsy progression [93].

Other markers currently being investigated include measures of cellular proliferation, such as proliferating cell nuclear antigen and Ki-67, micro RNAs, and single nucleotide polymorphisms. Early results have shown that urinary TMPRSS2:ERG and PCA3 accurately identify aggressive cancer as defined by tumor volume or Gleason score [94]. Recently, investigators found that expressed prostatic secretion biomarkers (total RNA and total specimen volume) obtained before RP outperformed TPMRESS2:ERG variants in predicting risk of pathologic upstaging or upgrading in men who were eligible for AS under NCCN guidelines [95]. Additionally, nomograms have successfully incorporated preoperative levels of serum transforming growth factor- $\beta$ 1 and interleukin 6-soluble receptor to identify those at risk of biochemical recurrence after prostatectomy [96]. The serum testosterone level may also be of prognostic value in AS populations, because men with low levels are at risk of harboring more aggressive disease [97]. The Prostate Active Surveillance Study, a multicenter cohort study, is currently enrolling AS candidates within nine large academic centers. Biological specimens will be collected for purposes of investigating potential serum and urinary biomarkers of disease progression to potentially identify AS patients who harbor higher risk disease [98].

Also emerging is the potential utility of multiparametric magnetic resonance imaging (MRI) as well as spectroscopy for identifying candidates and monitoring for disease progression in men who choose AS. A recent pilot study found that apparent diffusion coefficients accurately identified those who progressed to radical treatment [99]. Another study found that incorporation of MRI and magnetic resonance spectroscopy into a risk nomogram improved accuracy in predicting aggressive disease [100]. The greatest

utility of specialized MRI techniques may be as a complement or alternative tool to confirmatory biopsy. Investigators have found that MRI appears to have a high yield in predicting reclassification among men choosing AS, and positive and negative predictive values of 83% and 81%, respectively, were recently reported.

## CONCLUSIONS

PSA screening reduces prostate cancer mortality rates, but at the cost of overdiagnosis of low-risk, indolent tumors. However, AS is emerging as an attractive and safe management option for men with such low-risk features, thus allowing them to delay immediate treatment and its associated side effects until it is truly necessary. It is hopeful that new biomarkers and clinical tools will become available that will allow us to better identify those who can be safely managed with AS, thereby reducing the concern for overtreatment and its associated morbidity.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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