Curr Urol Rep (2017) 18: 48
DOI 10.1007/s11934-017-0702-y

Prostate Biopsy in Active Surveillance Protocols: Immediate Re-biopsy and Timing of Subsequent Biopsies

Jonathan H. Wang[1] · **Tracy M. Downs**[1,2] · **E. Jason Abel**[1,2] · **Kyle A. Richards**[1,2] · **David F. Jarrard**[1,2,3]

Published online: 6 June 2017

Abstract
Purpose of Review This manuscript reviews contemporary literature regarding prostate cancer active surveillance (AS) protocols as well as other tools that may guide the management of biopsy frequency and assess the possibility of progression in low-risk prostate cancer.
Recent Findings There is no consensus regarding the timing of surveillance biopsies; however, an immediate repeat biopsy within 12 months of diagnosis for patients considering AS confirms patients who have favorable risk disease yet also identifies patients who were undersampled initially. Studies regarding multiparametric MRI, nomograms, and biomarkers show promise in risk stratifying and counseling patients during AS. Further studies are needed to determine if these supplemental tests can decrease the frequency of surveillance biopsies.
Summary An immediate re-biopsy can help to reduce the risk of missing clinically significant disease. Other clinical tools, including mpMRI, exist that can be used as an adjunct to counsel patients and guide a personalized discussion regarding the frequency of surveillance biopsies.

This article is part of the Topical Collection on *Prostate Cancer*

✉ David F. Jarrard
jarrard@urology.wisc.edu

[1] Department of Urology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

[2] University of Wisconsin Carbone Comprehensive Cancer Center, Madison, WI, USA

[3] Environmental and Molecular Toxicology, University of Wisconsin, Madison, WI, USA

Keywords Prostate cancer · Active surveillance · Prostate biopsy · Repeat biopsy · Multiparametric MRI

Introduction

Prostate cancer is the second most frequently diagnosed form of cancer and the second leading cause of male cancer death in the USA with an estimated 26,730 deaths in 2017 [1, 2]. In randomized trials, screening for prostate cancer with prostate-specific antigen (PSA) reduces disease-specific mortality [3]. However, the low risk of death from prostate cancer prompts a debate regarding the diagnosis and overtreatment of clinically insignificant disease [4, 5].

Active surveillance (AS) has emerged as an important management strategy to monitor men with low-risk prostate cancer over time, intervening with curative intent only in patients with disease progression. While AS has been established as a management approach to allow many patients with prostate cancer to avoid the potential morbidity of treatment, the ability to appropriately risk stratify patients relies on the clinician's and pathologist's ability to accurately detect life-threatening cancer. Clinical and pathologic information, especially the Gleason score, are used for initial risk assessment. Additional tools such as molecular testing, imaging, and risk calculators have also been described to improve patient selection for small, well-differentiated, organ-confined disease that can be safely monitored with AS.

Scheduled, repeat prostate biopsies play a crucial role in monitoring patients on AS; however, there is no consensus on the timing, extent, or approach to limit the number of biopsy events. In a recent survey of urologists in the USA performing AS, 58% felt an initial repeat biopsy should be performed at 12 months, 30% recommended earlier repeat biopsy, and 12% typically waited until 15 to 26 months to perform another

biopsy [6]. Furthermore, compliance with recommended prostate biopsy remains an important issue, with only 13% of men getting a follow-up biopsy beyond 2 years in a community setting [7•]. This review summarizes contemporary literature regarding current AS protocols as well as imaging studies, genetic testing, and clinical tools that may guide the management of biopsy frequency in low-risk prostate cancer.

Contemporary Active Surveillance Protocols

AS has become a widely adopted approach of preventing intervention in many men with low-risk prostate cancer and primarily utilizes serial patient exams including digital rectal exam (DRE), PSA measurements, and periodic prostate biopsies. The rationale behind this approach is that men with more aggressive disease will be identified by physical exam, PSA, or histology at a time when intervention can still lead to cure, thereby avoiding overtreatment of clinically indolent disease and reducing treatment-related morbidity.

In general, AS is reserved for patients with lower risk disease. This clinical definition varies, however most criteria are based on the Epstein and NCCN criteria for clinically insignificant prostate cancer [8, 9]. Measures include clinical stage T1c, PSA <10, PSAD <0.15 ng/ml, Gleason score ≤ 6, ≤2 positive biopsy cores, and ≤50% involvement of any biopsy core. While these represent more stringent criteria, others suggest that stricter, more exclusive criteria do not necessarily result in significantly improved outcomes. In a recent study of 1085 patients, various AS criteria were applied, and there was no difference in terms of Gleason score upgrading, biochemical recurrence, or PSA velocity after treatment between patients who met more inclusive criteria and those who would have been excluded by stricter criteria [10]. Several different follow-up protocols exist as summarized in Table 1, however most recommend a mandatory confirmatory biopsy within 1 year of enrollment [11–17]. Different prospective AS trials recommend periodic PSA measurements and DRE follow-up testing every 3–6 months. The timing of subsequent prostate biopsies varies from 1 to 4 years, unless triggered by other concerning factors including rising PSA or changes in DRE [11–17].

Fear of missing clinically significant cancer with templated prostate biopsies is balanced by the desire to minimize the morbidity and frequency of biopsies. Part of the rationale for reducing the frequency of this procedure is to decrease risk of adverse events, which is especially important given the increasing rates of drug-resistant infections, which is the most common major complication associated with prostate biopsy [18]. Among 5192 patients undergoing AS, greater than 80% had 1 or more PSA tests per year, but fewer than 13% underwent biopsy beyond the first 2 years [7•]. Furthermore, while more frequent biopsies can reassure both the patient and the physician that more high-risk cancer is not present, it can

Table 1 Active surveillance monitoring protocols and triggers for intervention

Group	Active surveillance protocol					Findings prompting intervention			
	Confirmatory biopsy <12 months	PSA measurements	DRE	Repeat biopsy frequency	Targeted MRI biopsy	Gleason score	Positive scores	Maximal core involvement	PSA doubling time
Johns Hopkins	Yes	6 months	6 months	1 year	x	>6	>2	>50%	x
UCSF	Yes	6 months	6 months	1–2 years	x	>6	>33%	>50%	x
Sunnybrook, Toronto	Yes	3 months × 2 years, then 6 months	x	3–4 years	Changes in PSA kinetics or DRE	Any upgrading	x	x	<3 years
Göteborg	No	3–6 months	3–6 months	2–3 years	x	No strict criteria defined, but AS failure if progression in PSA, grade, or stage			
PRIAS (NTR1718)	Yes	3–6 months	x	Year 1, 3, and 7	>2 scores on standard biopsy	≥3 + 4	>2 (from saturation or MRI-guided biopsies)	x	<3 years
Canary PASS	Yes	3 months	6 months	6–12, 24, 48, 72 months	x	Any upgrading, sum, or primary	≥34%	x	x

UCSF University of California San Francisco, *PRAIS* Prostate Cancer Research International Active Surveillance, *PASS* Canary Prostate Active Surveillance Study

also be a source of frustration as most men undergoing repeat biopsies do not have cancer detected [19]. Many studies are currently focused on further risk stratifying patients at the time of diagnosis with the goal of reducing subsequent, unnecessary follow-up biopsies.

Immediate and Subsequent Biopsies in Active Surveillance

A cornerstone of AS is our ability to appropriately evaluate an individual patient's risk. In addition to PSA and DRE, the clinician relies on prostate biopsies to accurately identify low-volume, low-grade prostate cancer. In order to minimize risk misclassification and undersampling, 10–20 core prostate biopsies are generally performed. Most AS protocols recommend a repeat, confirmatory biopsy within the first 12–18 months that includes additional biopsies surrounding the involved region as well as other undersampled areas. In patients undergoing re-biopsy for elevated PSA, these areas include the anterior apex and lateral crescents of the prostate (Fig. 1) [20, 21].

Archival studies have shown that 32–44% of the time, final pathology at the time of radical prostatectomy is upgraded from the Gleason score 6 prostate cancer seen on biopsy [22, 23]. In specific AS cohorts, the Gleason score upgrading rates of 13.8, 21, and 15% have been found, with an increase in 8.9% in the recently reported PRIAS publication [11–17]. In our own experience, 17% of patients considering AS were upgraded at the first re-biopsy performed at <12 months [24•]. This rate may vary based on population factors including age, as well as the criteria used for AS entry with more strict criteria leading to lower upgrading rates. These findings demonstrate the innate imperfection of transrectal ultrasound (TRUS)-guided prostate biopsies in detecting significant cancer, and underscore the need for subsequent prostate biopsies during surveillance.

While upgrading at first re-biopsy is thought to be secondary to inadequate initial sampling, it remains unclear if patients who fail AS ultimately fail due to disease progression or due to improved detection. Conceptually, a templated TRUS biopsy has a low negative predictive value especially in larger glands. Studies have demonstrated that prostate cancer is often multifocal and 70–80% of patients who have unilateral disease on biopsy ultimately have bilateral, T2c disease on post prostatectomy pathology [25, 26]. While the initial biopsy core number > 18 has been correlated with a reduced risk of unrecognized cancer, increased prostate sampling may significantly increase patient discomfort [27, 28]. In some studies, 20 core biopsies performed on patients eligible for AS have been used to reduce the risk of undersampling patients and suggest that saturation biopsies may provide an improved assessment of the extent and grade of disease in men [29]. Conversely, other studies have shown that patients undergoing saturation biopsy are more likely to progress to treatment while on AS [30]. It is likely that patients who meet the AS criteria on saturation biopsy may be at lower risk, and the frequency of re-biopsy can safely extend.

Although the yield of repeat biopsies in diagnosing cancer decreases with each subsequent biopsy, we have previously demonstrated that an immediate (within 3–6 months), 12–14 core re-biopsy after the initial biopsy can provide valuable information in discriminating patients who are considering AS [24•, 31]. Based on these findings, at our institution, a re-biopsy within 6 months after diagnosis is performed for all patients considering AS after diagnosis of low-risk prostate cancer to not only confirm men who have favorable risk disease, but also to identify patients who were understaged initially and select for patients who may benefit from earlier curative intervention. In some situations, especially with larger gland size over 30cm^3 or in younger patients, MRI is now being used to further inform this repeat strategy. In a study looking at the ability of MRI-guided repeat biopsy to further risk stratify patients with Gleason 3 + 3 prostate cancer on active surveillance, at least 1 in 5 men experienced Gleason score upgrading when biopsies were performed guided by the presence of a suspicious MRI lesions with PSA density < 0.15 ng/mL/mL and PI-RADS score < 3 predicting no Gleason score upgrading [32]. These studies suggest that low-risk prostate MRI and lower PSA density may reduce the frequency of unnecessary follow-up biopsy procedures in men on AS.

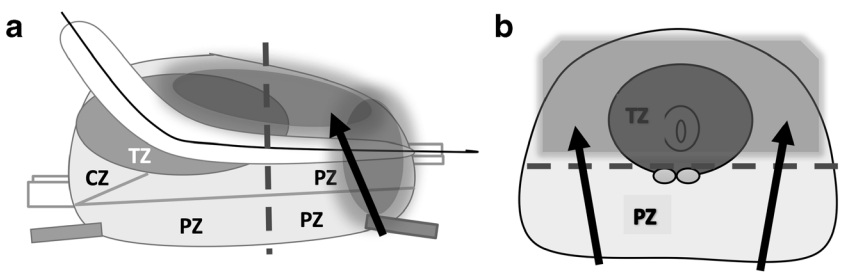

Fig. 1 Undersampled regions in patients with elevated PSAs and negative biopsies can harbor cancer in patients with focal low-risk disease. If there is concern for clinically significant prostate cancer, areas that should be targeted and have higher yield on repeat biopsy include the anterior apex of the prostate (**a**), as well as the lateral crescents (**b**). *PZ* peripheral zone, *CZ* central zone, *TZ* transitional zone

As seen in the various follow-up protocols (Table 1), the optimal timing of subsequent biopsies after the first re-biopsy varies between institutions. One recommendation is that a repeat biopsy be performed within the first year. Additional factors may be used to more accurately risk stratify patients with the goal of reducing the number of subsequent unnecessary biopsies.

Clinicopathologic Tools for Calculating Risk of Progression

Previous studies have suggested that patients with negative first repeat biopsies are at lower risk of disease progression than those with a positive first repeat biopsy (11 vs. 40%) [33]. Similarly, a positive confirmatory biopsy was recently suggested to be the only predictor of disease progression during AS [34]. In our experience, over half (53%) of patients considering AS undergoing immediate repeat prostate biopsy had no cancer detected, with 17% of patients being upgraded, and the remainder demonstrating no change [24•]. When evaluating the patterns of positive and negative biopsies in AS, men with repeatedly negative biopsies likely harbor insignificant disease, with only 3% of men progressing at the fourth prostate biopsy after a negative second and third compared to 9% progression with a positive second biopsy [35]. On multivariable logistic regression, a negative confirmatory biopsy result was independently associated with a decreased risk of progression (odds ratio [OR] 0.28; 95% confidence interval [CI], 0.11–0.70; $P < .01$) [35]. This repeat biopsy information can be used to adjust the timing for follow-up biopsies. At our institution based on this data, if no cancer is detected on a confirmatory biopsy, we begin to space out the timing of follow-up biopsies as they appear to be at lower risk of disease progression. The details of subsequent biopsies can help to further delineate risk and in a subset of patients, this information can be applied to decrease frequency of surveillance biopsies.

Numerous studies have demonstrated the prognostic value of PSA density in choosing candidates for AS [36]. Studies monitoring patients on AS have demonstrated that the PSA density can also be of use in predicting failure. Recent studies have shown that PSA density of >0.15 ng/mL/mL is an important predictor for disease progression [37]. In a study of 242 men with three or more biopsies and ≥3 years of follow-up, the PSA density was associated with the risk of progression (OR 2.35; 95% CI, 1.31–4.22; $P < .01$) [35]. In the Canary Prostate Active Surveillance Study (PASS) trial, 421 men experienced reclassification at the first AS biopsy, and PSA density ≥ 0.15 (OR 1.9, 95% CI 1.1, 4.1) and body mass index ≥35 kg/m^2 (OR 2.4, 95% CI 1.1–5.7) was associated with increased odds of reclassification [17].

While immediate re-biopsy when considering AS can help mitigate concerns of undetected, more aggressive, and higher grade disease, the true biology of prostate cancer is difficult to predict based on prostate biopsy alone [23, 38]. Many prognostic models have been developed to attempt to estimate the probability of disease progression at the time of surgery, based on clinicopathologic characteristics. While nomograms traditionally are used to provide useful information regarding a patient's risk for harboring indolent verses aggressive disease at the time of radical prostatectomy, these retrospective models can also estimate disease in the AS setting.

Several recent studies have evaluated the performance of radical prostatectomy-based prognostic tools in various AS cohorts. Wang et al. compared the Kattan, Steyerberg, Nakanishi, and Chun nomograms ability to predict biopsy progression in an AS cohort of 273 patients. In their study, these nomograms had only modest ability to predict AS failure, with area under the curve ranging from 0.52 to 0.67 [39]. These nomograms were developed based on higher risk populations who underwent prostatectomy, and many rely on PSA, which has been shown to be a poor predictor of Gleason score upgrading [40]. At our institution, Truong et al. developed and externally validated the Biopsy-Integrated Algorithm for Determining Gleason 6 Upgrading Risk (BADGR) [41]. This nomogram differs from others in that it was developed from an initial population of low-risk patients with Gleason 6 prostate cancer on initial biopsy who then underwent radical prostatectomy. In addition, it incorporates PSA density which may more accurately predict the risk of progression [40]. Importantly, this nomogram was validated in multiple external populations [41]. Using this nomogram, we have been able to generate an upgrading risk (UR) which shows promise in being used as an adjunct in predicting pathologic AS failure [42•]. When the BADGR nomogram was compared to Partin and Dinh tables, as well as the Kattan and Kulkarni nomograms, Iremashvili et al. found that only the BADGR and Kattan nomograms could provide adequate performance in predicting biopsy progression [43••].

Although these models have shown value in predicting AS failure, they have not been broadly integrated into AS protocols but remain useful tools to help risk stratify and counsel patients. One advantage of these nomograms is that benefit may be generated at no additional cost in contrast to other strategies employing molecular or radiologic approaches. With more research, these may be incorporated with other tools to help differentiate patients who are at higher risk that need more frequent biopsies.

Non-PSA-Based Biomarkers and Molecular Testing in Active Surveillance

The PSA test has undergone significant scrutiny in its role as a tumor marker for prostate cancer. While PSA screening can decrease disease-specific mortality, its lack of specificity makes it a poor predictor of overall tumor aggressiveness [40]. Many efforts have been made to develop non-PSA-based tests to detect prostate cancer, and several have shown some preliminary promise in predicting disease progression on AS (Table 2).

The prostate cancer antigen 3 (PCA3) tests for non-coding RNA in the urine after a prostatic massage. Some studies have shown higher specificity for prostate cancer than serum PSA, and it is currently FDA-approved for patients with a negative biopsy who are considering further evaluation [44]. However, when applied to AS patients, its utility has been controversial. A study from John Hopkins found that when corrected for age and diagnosis date, PCA3 could not be used to predict biopsy progression [45]. Another urine marker that has shown possible utility is a gene fusion between transmembrane protease serine 2 and the ERG transcriptional regulator (TMPRSS2–ERG). In the Canary PASS trial, urinary PCA3 and TMPRSS2–ERG levels collected at the time of enrollment to AS were correlated with higher volume and higher Gleason score prostate cancer; OR 1.67 (95% CI 1.10–2.52; $P = 0.02$) for PCA3 and OR 1.24 (95% CI 1.01–1.53; $P = 0.05$) for TMPRSS2:ER [46]. Furthermore, ERG expression in prostate biopsy tissue has also been found to have a 2.45-fold increased risk of disease progression while on AS at 2 years [47].

Commercial tests have also been developed that show promise in risk stratifying patients for AS based on the biopsy cancer tissue. The Prolaris® test which measures the ratio of gene expression in 46 various cell cycle progression and housekeeping genes generates a cell cycle progression score. This score has been shown to be able to predict disease aggressiveness and generate a prostate cancer mortality risk, as well as predict adverse pathology and biochemical recurrence following treatment with prostatectomy or radiation [48–51]. Similarly, OncotypeDx® is another genomic assay performed on biopsy tissue which measures 17 various genes involved in four different pathways associated with prostate cancer to generate a genomic prostate score. This test predicts the likelihood of low-grade and organ-confined disease in patients undergoing treatment with prostatectomy despite tumor heterogeneity and under sampling at the time of biopsy [52, 53]. While both tests can predict the presence of higher grade cancers and have generated excitement in their ability to counsel patients regarding treatment versus AS, neither has been applied to cohorts currently undergoing AS. It remains to be seen if these tests can be used serially during AS, or if patients with lower risk scores from these genomic tests can be safely monitored with decreased biopsy frequency.

These non-invasive markers show promise; however, more studies are needed to assess their role either alone or in combination in risk stratifying patients during AS and refining biopsy follow-up.

Impact of Multiparametric MRI in Enhancing Prostate Cancer Detection

In the last several years, MRI technology has progressed to the point of enabling many established prostate cancer lesions to be visualized and characterized. Advancements in multiparametric MRI (mpMRI) consisting of T1, T2, diffusion weighted imaging (DWI), and dynamic contrast enhancement (DCE) have shown promise in detecting higher grade, higher volume cancers [54]. In addition, increased magnet strength to 3.0 T (and higher) has improved MRI resolution and reduced the need for an endorectal coil. While interpreting the multiple sequences involves a

Table 2 Non-PSA-based markers for prostate cancer

Marker	Description	Marker utility
PCA3	Non-coding RNA expressed solely in the prostate, measured in the urine	Increased specificity for prostate cancer compared to PSA; non-invasive test, however utility in predicting AS reclassification is controversial
TMPRSS2–ERG	Serine protease fusion gene measured in the urine	Levels are increased in patients with prostate cancer; non-invasive and can be useful in identifying patients with higher risk disease during active surveillance. These patients may require more frequent biopsies
Prolaris ®	Measures the gene expression of 31 cell cycle progression genes and 15 housekeeping genes on prostate biopsy samples	Can predict prostate cancer-specific mortality and adverse features at time of prostatectomy; low scores can possibly be used to space out biopsies
OncotypeDx®	Measures the gene expression of 17 genes involved in androgen signaling, cellular organization, stromal response, and cellular proliferation on prostate biopsy samples	Can predict the presence of adverse pathology and is useful in counseling patients towards treatment versus active surveillance; absence of high risk pathology might flag patients who can have less intense biopsy regimens

significant learning curve, in the hands of an experienced radiologist, the new Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) reporting scheme has been developed to assess risk of clinically significant prostate cancer [55]. Prostate lesion scores from 1 to 5 to designate risk, with PI-RADS 1 representing "very low", and 5 representing "very high" risk. Recently, the American Urologic Association in conjunction with the Society for Abdominal Radiology released a consensus statement, recommending prostate MRI for any patient with prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy [56].

Although mpMRI can identify suspicious lesions, prostate biopsies still must be performed to guide AS protocols. "Cognitive" MRI-guided biopsies can be rapidly incorporated into clinical practice. This entails a TRUS-guided biopsy aimed at the area of interest visualized on a previously reviewed MRI. This generates reasonable sensitivity in the hands of an experienced urologist [57••]. Newer MRI-US fusion devices are available, in which a three-dimensional reconstruction of the prostate and lesion can be overlaid with real-time ultrasound and biopsy needle tracking. In the recent PROFUS trial, a prospective, blinded comparison between visual, cognitive targeting to fusion biopsies, the fusion biopsies were able to better detect smaller lesions [57••]. In a prospective study in AS patients, UroNav fusion-targeted biopsy was 6.3 times more likely to yield a core positive for Gleason 7 cancer compared with TRUS only (25% of 141 versus 4% of 874, $P < 0.001$) suggesting increased ability to detect clinically significant prostate cancer [58]. However, these platforms are costly, require significant time that is not reimbursed, and require close coordination between radiologists and urologists.

Critical analysis of mpMRI has shown that this technology can be useful in risk stratifying patients based on lesion size, extent, and potentially even predict histologic grade. Studies have identified limitations to mpMRI, which has been shown to have a good negative predictive value and moderate positive predictive value [59, 60]. PI-RADS v2 scores of 4–5 correctly identify 94–95% of tumors of any Gleason score > 0.5 mL, but is limited in its detection of even Gleason 4 + 3 tumors <0.5 mL [61, 62]. In a recent study comparing mpMRI to radical prostatectomy, over 20% of significant lesions were missed [63]. When comparing mpMRI and final radical prostatectomy pathology, MRI also has a positive predictive value of 91.2% in predicting organ-confined disease and a negative predictive value for extracapsular extension of 89.6% [64]. Thus, while MRI is able to accurately detect larger and higher grade tumors, it is limited in its ability to detect smaller lesions that may be present in AS patients. Nevertheless, it can still be useful in surgical planning and have utility in monitoring disease progression in future AS protocols.

MRI shows promise in playing a larger role in AS, but it has not yet been uniformly applied to AS protocols. Starting in 2009, the Sunnybrook, Toronto cohort began to integrate mpMRI with their protocol to evaluate those with concerning PSA kinetics [12]. While their studies are preliminary, due to the success and safety of current AS protocols, up to 55% of patients avoided any treatment, without the benefit from MRI [12]. In the newest PRIAS protocol, a modification was made in 2015, where mpMRI with a targeted biopsy began to supplant switching to treatment [16]. In a small study, MRI demonstrated progression in an AS population in 14 (12%) of 114 patients and findings of extracapsular extension in 9 of these patients [65]. Compelling data is accumulating for a role for MRI in the initial evaluation of patients being considered for AS. We have also begun using serial mpMRI during AS in our own practice to reduce the need for biopsies especially in AS patients beyond 2 years of follow-up.

Is There an End to Active Surveillance and Repeat Biopsies?

AS is useful in the management of low-risk prostate cancer patients as it avoids treatment morbidity while still providing the ability to offer potentially curative treatment to those who progress. These criteria for AS progression are outlined in Table 1. Watchful waiting (WW) is another strategy that aims to manage symptoms of prostate cancer progression in older patients with substantial comorbidities and limited life expectancy. As patients are monitored on AS protocols over time, many patients will not progress, and their life expectancy will change to a point where curative treatment is no longer indicated. At this point, a switch to watchful waiting is made, with less frequent follow-up and possibly no further prostate biopsies. The time point in which to switch from AS to WW is not clearly defined and the decision is based on complex patient-centered discussions. Due to the personalized nature of these assessments, attempts have been made to better characterize trends in this transition. In a Swedish population of 7356 people over a 10-year period, 48% of men with very low-risk prostate cancer were eventually switched from AS to WW. When stratified by age, 10% of 55-year-old men switched to WW, and 50% of otherwise healthy 70-year-old men switched [66].

The decision to switch is often made based on a patient's age and comorbidities, at a point where "curative intervention" may not improve life expectancy. In a 23-year-follow-up study of 695 men randomized to watchful waiting or surgery, men older than 65 years of age at diagnosis had no reduction in mortality with radical prostatectomy; however, they did have a decreased risk of metastasis and need for palliative treatment [67]. Men younger than 65 had a reduction in prostate cancer-specific death after surgery [67]. In 2017, the International Society of Geriatric Oncology

(SIOG) released updated guidelines on the management of prostate cancer in patients >70 years old [68••]. They strongly emphasize the heterogeneity of elder patients, and that these patients should be managed according to their individual health status and not according to chronologic age. While comprehensive geriatric assessment tools exist, they are often time-intensive and require specialists. The SIOG recommends a short eight question (G8) assessment for geriatric patients. This screening tool is recommended in the European Association of Urology (EAU) guideline for management of prostate cancer, and studies have shown that low G8 scores strongly predict mortality [69, 70]. This questionnaire evaluates food intake, weight loss, mobility, neuropsychological problems, BMI, number of prescription drugs taken, self-assessment of health, and age. This screening tool can quickly stratify patients into "fit" patients who will tolerate and may benefit from any treatment, and those who are "frail", who deserve further geriatric assessment [68••].

While many studies demonstrate the benefits of watchful waiting and active surveillance, the psychological burden of AS and WW is also being studied, and patient preference must be factored into the decision to continue AS. One study found that 9% of patients discontinued AS on their own, due to either fear of cancer or anxiety associated with the uncertainty of biopsy results [71]. In our unpublished experience, we found that 12% of patients elected to pursue definitive treatment over continued AS out of anxiety, rather than reclassification from biopsy results. In community practice, this burden was emphasized in the SEER (Surveillance, Epidemiology and End Results)-Medicare database where only 5–11% of patients adhered to the frequency of monitoring recommended by major prospective AS programs [7•].

Ultimately, the discussion of when to switch to watchful waiting should be driven by the urologist's desire to minimize morbidly to the patient. Continued education of both patients and physicians will help providers make appropriate clinical decisions that maximize patient quality of life without impacting survival.

Conclusions

An early repeat biopsy in patients considering AS can help to reduce the risk missing clinically significant cancer, and more accurately identify patients who would benefit from treatment. MRI is also a useful adjunct for improving the detection of clinically significant disease in this population and may be used to decrease the biopsy rates in patients undergoing longer term follow-up. In addition, nomograms and non-PSA-based markers are valuable tools that can help risk stratify a patient's disease. However, until further studies are able to delineate the risks, benefits, and cost effectiveness of these tools in guiding patients towards more or less frequent biopsies, urologists should familiarize themselves with the utility of each in order to better counsel patients.

Compliance with Ethical Standards

Conflict of Interest Jonathan H. Wang, Tracy M. Downs, E. Jason Abel, Kyle A. Richards, and David F. Jarrard each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7–30.
2. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, Bray F. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012;61:1079–92.
3. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384:2027–35.
4. Heijnsdijk EAM, der Kinderen A, Wever EM, Draisma G, Roobol MJ, de Koning HJ. Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. Br J Cancer. 2009;101:1833–8.
5. Siegel R, Miller K, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:29.
6. Gorin MA, Eldefrawy A, Ekwenna O, Soloway MS. Active surveillance for low-risk prostate cancer: knowledge, acceptance and practice among urologists. Prostate Cancer Prostatic Dis. 2012;15:177–81.
7. • Loeb S, Walter D, Curnyn C, Gold HT, Lepor H, Makarov DV. How active is active surveillance? Intensity of followup during active surveillance for prostate cancer in the United States. J Urol. 2016;196:721–6. **This SEER database review demonstrates the difficulty of having patients comply with rigorous active surveillance protocol.**
8. Kryvenko ON, Carter HB, Trock BJ, Epstein JI. Biopsy criteria for determining appropriateness for active surveillance in the modern era. Urology. 2014;83:869–74.
9. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 1.2014. J Natl Compr Cancer Netw. 2013;11:1471–9.
10. Komisarenko M, Timilshina N, Richard PO, Alibhai SMH, Hamilton R, Kulkarni G, Zlotta A, Fleshner N, Finelli A. Stricter active surveillance criteria for prostate cancer do not result in significantly better outcomes: a comparison of contemporary protocols. J Urol. 2016;196:1645–50.
11. Tosoian JJ, Mamawala M, Epstein JI, Landis P, Wolf S, Trock BJ, Carter HB. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol. 2015;33:3379–85.
12. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, Yamamoto T, Mamedov A, Loblaw A. Long-term follow-up of a

large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33:272–7.
13. Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Göteborg randomised population-based prostate cancer screening trial. Eur Urol. 2013;63:101–7.
14. Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J Urol. 2015;193:807–11.
15. Selvadurai ED, Singhera M, Thomas K, Mohammed K, Woode-Amissah R, Horwich A, Huddart RA, Dearnaley DP, Parker CC. Medium-term outcomes of active surveillance for localised prostate cancer. Eur Urol. 2013;64:981–7.
16. Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, Roobol MJ, group. for the P study. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. Eur Urol. 2016;70:954–60.
17. Macleod LC, Ellis WJ, Newcomb LF, et al. Timing of adverse prostate cancer reclassification on first surveillance biopsy: results from the Canary Prostate Cancer Active Surveillance Study. J Urol. 2016; doi:10.1016/j.juro.2016.10.090.
18. Aly M, Dyrdak R, Nordström T, Jalal S, Weibull CE, Giske CG, Grönberg H. Rapid increase in multidrug-resistant enteric bacilli blood stream infection after prostate biopsy—a 10-year population-based cohort study. Prostate. 2015;75:947–56.
19. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, Freedland SJ, Klotz LH, Parker C, Soloway MS. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol. 2012;62:976–83.
20. Zaytoun OM, Jones JS. Prostate cancer detection after a negative prostate biopsy: lessons learnt in the Cleveland Clinic experience. Int J Urol. 2011;18:557–68.
21. Giulianelli R, Brunori S, Gentile BC, et al. Saturation biopsy technique increase the capacity to diagnose adenocarcinoma of prostate in patients with PSA< 10 ng/ml, after a first negative biopsy. Arch Ital di Urol Androl organo Uff [di] Soc Ital di Ecogr Urol e Nefrol. 2011;83:154–9.
22. Lee MC, Dong F, Stephenson AJ, Jones JS, Magi-Galluzzi C, Klein EA. The Epstein criteria predict for organ-confined but not insignificant disease and a high likelihood of cure at radical prostatectomy. Int Braz J Urol. 2011;37:123–4.
23. Dinh KT, Mahal BA, Ziehr DR, et al. Incidence and predictors of upgrading and up staging among 10,000 contemporary patients with low risk prostate cancer. J Urol. 2015;194:343–9.
24.• King AC, Livermore A, Laurila TAJ, Huang W, Jarrard DF. Impact of immediate TRUS rebiopsy in a patient cohort considering active surveillance for favorable risk prostate cancer. Urol Oncol Semin Orig Investig. 2013;31:739–43. **This paper supports the use of an immediate, confirmatory biopsy in patients considering active surveillance, to reduce the risk of undersampling.**
25. Briganti A, Tutolo M, Suardi N, et al. There is no way to identify patients who will harbor small volume, unilateral prostate cancer at final pathology. Implications for focal therapies prostate. 2012;72:925–30.
26. Gallina A, Maccagnano C, Suardi N, et al. Unilateral positive biopsies in low risk prostate cancer patients diagnosed with extended transrectal ultrasound-guided biopsy schemes do not predict unilateral prostate cancer at radical prostatectomy. BJU Int. 2012;110:E64–8.
27. Capitanio U, Karakiewicz PI, Valiquette L, et al. Biopsy core number represents one of foremost predictors of clinically significant Gleason sum upgrading in patients with low-risk prostate cancer. Urology. 2009;73:1087–91.
28. Jones JS. Saturation biopsy for detecting and characterizing prostate cancer. BJU Int. 2007;99:1340–4.
29. Abouassaly R, Lane BR, Jones JS. Staging saturation biopsy in patients with prostate cancer on active surveillance protocol. Urology. 2008;71:573–7.
30. Thompson JE, Hayen A, Landau A, Haynes A-M, Kalapara A, Ischia J, Matthews J, Frydenberg M, Stricker PD. Medium-term oncological outcomes for extended vs saturation biopsy and transrectal vs transperineal biopsy in active surveillance for prostate cancer. BJU Int. 2015;115:884–91.
31. Roehl KA, Antenor JAV, Catalona WJ. Serial biopsy results in prostate cancer screening study. J Urol. 2002;167:2435–9.
32. Alberts AR, Roobol MJ, Drost F-JH, van Leenders GJ, Bokhorst LP, Bangma CH, Schoots IG. Risk-stratification based on magnetic resonance imaging and prostate-specific antigen density may reduce unnecessary follow-up biopsy procedures in men on active surveillance for low-risk prostate cancer. BJU Int. 2017; doi:10.1111/bju.13836.
33. Patel MI, Deconcini DT, Lopez-Corona E, Ohori M, Wheeler T, Scardino PT. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. J Urol. 2004;171:1520–4.
34. Adamy A, Yee DS, Matsushita K, Maschino A, Cronin A, Vickers A, Guillonneau B, Scardino PT, Eastham JA. Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. J Urol. 2011;185:477–82.
35. Cary KC, Cowan JE, Sanford M, Shinohara K, Perez N, Chan JM, Meng MV, Carroll PR. Predictors of pathologic progression on biopsy among men on active surveillance for localized prostate cancer: the value of the pattern of surveillance biopsies. Eur Urol. 2014;66:337–42.
36. Tseng KS, Landis P, Epstein JI, Trock BJ, Carter HB. Risk stratification of men choosing surveillance for low risk prostate cancer. J Urol. 2010;183:1779–85.
37. Barayan GA, Brimo F, Bégin LR, Hanley JA, Liu Z, Kassouf W, Aprikian AG, Tanguay S. Factors influencing disease progression of prostate cancer under active surveillance: a McGill University Health Center cohort. BJU Int. 2014;114:E99–E104.
38. Schiffmann J, Wenzel P, Salomon G, et al. Heterogeneity in D'Amico classification–based low-risk prostate cancer: differences in upgrading and upstaging according to active surveillance eligibility. Urol Oncol Semin Orig Investig. 2015;33:329.e13–9.
39. Wang S-Y, Cowan JE, Cary KC, Chan JM, Carroll PR, Cooperberg MR. Limited ability of existing nomograms to predict outcomes in men undergoing active surveillance for prostate cancer. BJU Int. 2014;114:E18–24.
40. Loeb S, Bruinsma SM, Nicholson J, Briganti A, Pickles T, Kakehi Y, Carlsson SV, Roobol MJ. Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. Eur Urol. 2015;67:619–26.
41. Truong M, Slezak JA, Lin CP, et al. Development and multi-institutional validation of an upgrading risk tool for Gleason 6 prostate cancer. Cancer. 2013;119:3992–4002.
42.• Blute ML, Shiau JM, Truong M, Shi F, Abel EJ, Downs TM, Jarrard DF. A biopsy-integrated algorithm for determining Gleason 6 upgrading risk stratifies risk of active surveillance failure in prostate cancer. World J Urol. 2016; doi:10.1007/s00345-016-1933-0. **This article applies a biopsy-driven nomogram in predicting upgrading risk during active surveillance.**
43.•• Iremashvili V, Manoharan M, Kava BR, Parekh DJ, Punnen S. Predictive models and risk of biopsy progression in active surveillance patients. Urol Oncol Semin Orig Investig. 2017;35:37.e1–8. **This review compares various normograms and their ability to predict progression of cancer during active surveillance.**

44. Goode RR, Marshall SJ, Duff M, Chevli E, Chevli KK. Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients. Prostate. 2013;73:48–53.
45. Tosoian JJ, Loeb S, Kettermann A, Landis P, Elliot DJ, Epstein JI, Partin AW, Carter HB, Sokoll LJ. Accuracy of PCA3 measurement in predicting short-term biopsy progression in an active surveillance program. J Urol. 2010;183:534–8.
46. Lin DW, Newcomb LF, Brown EC, et al. Urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the Canary Prostate Active Surveillance Study. Clin Cancer Res. 2013;19:2442–50.
47. Berg KD, Vainer B, Thomsen FB, Røder MA, Gerds TA, Toft BG, Brasso K, Iversen P. ERG protein expression in diagnostic specimens is associated with increased risk of progression during active surveillance for prostate cancer. Eur Urol. 2014;66:851–60.
48. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br J Cancer. 2012;106:1095–9.
49. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol. 2014;192:409–14.
50. Koch MO, Cho JS, Kaimakliotis HZ, Cheng L, Sangale Z, Brawer M, Welbourn W, Reid J, Stone S. Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. Cancer Biomarkers. 2016;17:83–8.
51. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol. 2013;31:1428–34.
52. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol. 2014;66:550–60.
53. Brand TC, Zhang N, Crager MR, et al. Patient-specific meta-analysis of 2 clinical validation studies to predict pathologic outcomes in prostate cancer using the 17-gene genomic prostate score. Urology. 2016;89:69–75.
54. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, Taneja SS, Thoeny H, Villeirs G, Villers A. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol. 2015;68:1045–53.
55. Kasel-Seibert M, Lehmann T, Aschenbach R, Guettler FV, Abubrig M, Grimm M-O, Teichgraeber U, Franiel T. Assessment of PI-RADS v2 for the detection of prostate cancer. Eur J Radiol. 2016;85:726–31.
56. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol. 2016;196:1613–8.
57.•• Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng F-M, Melamed J, Taneja SS. A prospective, blinded comparison of magnetic resonance (MR) imaging–ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. Eur Urol. 2014;66:343–51. **This prospective, blinded study confirms that ultrasound fusion biopsies are better able to detect cancer than visual, cognitive biopsies.**
58. Da Rosa MR, Milot L, Sugar L, Vesprini D, Chung H, Loblaw A, Pond GR, Klotz L, Haider MA. A prospective comparison of MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance. J Magn Reson Imaging. 2015;41:220–5.
59. Thompson JE, van Leeuwen PJ, Moses D, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol. 2016;195:1428–35.
60. Wysock JS, Mendhiratta N, Zattoni F, Meng X, Bjurlin M, Huang WC, Lepor H, Rosenkrantz AB, Taneja SS. Predictive value of negative 3T multiparametric magnetic resonance imaging of the prostate on 12-core biopsy results. BJU Int. 2016;118:515–20.
61. Vargas HA, Hötker AM, Goldman DA, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. Eur Radiol. 2016;26:1606–12.
62. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol. 2011;186:1818–24.
63. Le JD, Tan N, Shkolyar E, Lu DY, Kwan L, Marks LS, Huang J, Margolis DJA, Raman SS, Reiter RE. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol. 2015;67:569–76.
64. Gupta RT, Faridi KF, Singh AA, Passoni NM, Garcia-Reyes K, Madden JF, Polascik TJ. Comparing 3-T multiparametric MRI and the Partin tables to predict organ-confined prostate cancer after radical prostatectomy. Urol Oncol Semin Orig Investig. 2014;32:1292–9.
65. Habibian DJ, Liu CC, Dao A, Kosinski KE, Katz AE. Imaging characteristics of prostate cancer patients who discontinued active surveillance on 3-T multiparametric prostate MRI. Am J Roentgenol. 2017;208:564–9.
66. Van Hemelrijck M, Garmo H, Lindhagen L, Bratt O, Stattin P, Adolfsson J. Quantifying the transition from active surveillance to watchful waiting among men with very low-risk prostate cancer. Eur Urol. 2016; doi:10.1016/j.eururo.2016.10.031.
67. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014;370:932–42.
68.•• Droz J-P, Albrand G, Gillessen S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the International Society of Geriatric Oncology. Eur Urol. 2017; doi:10.1016/j.eururo.2016.12.025. **This article represents the latest guidelines on approaching prostate cancer treatment in the geriatric population.**
69. Mottet N, Bellmunt J, Bolla M, et al. EAU–ESTRO–SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2016; doi:10.1016/j.eururo.2016.08.003.
70. Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients: the oncodage prospective multicenter cohort study. PLoS One. 2014; doi:10.1371/journal.pone.0115060.
71. Berger ZD, Yeh JC, Carter HB, Pollack CE. Characteristics and experiences of patients with localized prostate cancer who left an active surveillance program. Patient - Patient-Centered Outcomes Res. 2014;7:427–36.