Review Article

Indications for and transitioning to secondary treatment while on active surveillance for prostate cancer

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Abstract: For men with lower risk prostate cancer, there is ever-growing literature that demonstrates the oncologic safety of deferring radical treatment and opting for regular monitoring for disease progression. This strategy's success is largely owed to appropriate, systematic monitoring protocols that typically employ various prostate specific antigen (PSA) metrics or digital rectal exam (DRE) findings. Novel biologic markers and advanced imaging techniques have shown promise in active surveillance (AS) populations such as for use of patient candidacy as well as detection of disease progression. This review summarizes contemporary surveillance protocols as well as the emerging technologies which demonstrate significant potential to improve such protocols.

Keywords: Active surveillance (AS); low risk prostate cancer; biomarkers; multi-parametric magnetic resonance imaging

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Introduction

Active surveillance (AS) has been increasingly accepted over the last two decades as an option for managing men with localized, low risk prostate cancer (1). Central to the safety of AS is appropriate patient selection and careful disease monitoring to identify early signs of changing risk, or "triggers", for further intervention with curative intent. Multiple centers have published results with AS and utilize varying monitoring strategies (2-10). In addition to different surveillance strategies, these experiences describe different clinical triggers for recommending definitive local therapy. Understanding this decision to abandon surveillance for more definitive therapy represents an important clinical challenge.

Monitoring low risk prostate cancer for early signs of disease progression

Methods to actively monitor and identify early signs of changing disease risk are central to managing any patient with AS. Although there are no standard guidelines, most published protocols recommend periodic prostate specific antigen (PSA) measurement and repeat prostate biopsy. The American Society for Clinical Oncology (ASCO) has endorsed previously issued AS monitoring guidelines described by Cancer Care Ontario (11) in Canada. This includes PSA every 3–6 months, annual digital rectal exam (DRE), 12-core prostate biopsy every 2–5 years, and may include other "investigatory" measures such as imaging and/or biomarkers. *Table 1* describes surveillance strategies of contemporary North American and European AS cohorts. The role for surveillance prostate imaging with either standard ultrasound or mp-MRI remains unclear. While some experiences with stringent inclusion criteria may recommend treatment for any changes in tumor volume (including additional biopsy cores positive for cancer or increased percent core involvement) or changes in Gleason score (GS), others may recommend intervention only after

Table 1 Active surveillance series' selection and monitoring criteria

Institution	Study years	Selection criteria	Number enrolled [%*]	Median follow up	Surveillance Strategy	Primary intervention trigger(s)	PSA/PSA kinetics, % prog	Grade/ volume, % prog
Johns Hopkins	2014 (1)	T1c; Gleason ≤3+3=6; PSAd ≤0.15; max 2 positive cores	1,298 [71]	5 years	Semiannual PSA, DRE; annual biopsy	Surveillance biopsy no longer meets selection criteria; patient request	n/a	36
University of Toronto	2013 (2)	T1c; PSA ≤10–15; Gleason ≤3+3=6	993 [100]	6.4 years	PSA every 3 months for 2 years, then every 6 mo. Confirmatory biopsy within 12 months and then every 3-4 years unit age 80	PSA DT <3 years^^	11.7	10
UCSF	2011 (3) 2008 (4)	T1 or T2a, PSA ≤10; Gleason ≤3+3=6; <33% positive cores	640 [59]	47 months	DRE, PSA every 3 months, TRUS every 6–12 months, biopsy every 12–24 months	Gleason upgrade; increase in PSA-V of 0.75 ng/mL per year	5 of 11*	35
Royal Marsden	2011 (5)	Age 50–80 years, cT1/T2, PSA <15, Gleason >7 (3+4 permitted in men >65); percent pos cores ≤50%	499 [94]	5.7 years	DRE, PSA every 3 months for first year, then 4 months intervals 2nd year, then 6 months; confirmatory biopsy 1.5–2 years, then every 2 years	PSA-V >1 ng/mL/year; repeat biopsy with primary Gleason ≥4 or >50% positive cores	12	25
North America multi institution	2013 (6)	≤75 years, PSA ≤10, cT1-T2a, ≤ Gleason 6, max 3 biopsy cores positive	262 [100]	29 months	DRE and PSA every 6–12 months, Biopsy within 18 months of starting AS and then every 1–3 years. Some centers offered MRI	Increasing PSA, change in DRE, MRI findings	5	19
PRIAS Multicenter European study	2012 (7)	T1c or T2; PSA ≤10; Gleason ≤6; PSAd <0.2; max 2 positive cores	2,494 [100]	1.6 years	PSA every 3 months for first 2 years then every 6 months. Repeat biopsy 1, 4, 7 years	Gleason score >6 or >2 positive biopsy cores; PSA DT <3 years**	3^	28
Goteburg	2010 (8)	Age 50–64 years diagnosed after enrollment in Goteburg screening trial	439 [78]	6 years	PSA every 3–6 months; repeat biopsy if <2 mm cancer core; biopsy every 2–3 years	Progression in PSA, grade or stage	10	17.5

*, percent who met criteria; **, only if >1 year follow up; ^, includes only PSA DT <3 years in those who received definitive therapy; ^^, beginning in 2009, adverse PSA kinetics discontinued as sole trigger. PSA, prostate specific antigen; PSAd, prostate specific antigen density; PSA DT, prostate specific antigen doubling time; UCSF, University of California San Franciso; MSKCC, Memorial Sloan Kettering Cancer Center; PRIAS, Prostate Cancer Research International Active Surveillance.

change from low to intermediate risk disease.

PSA kinetics in the form of PSA velocity (PSAV) or PSA doubling time (PSA DT) have been utilized and studied for disease monitoring. Much of this is based on the association between PSA kinetics and cancer specific mortality after radiation or surgery (12,13). In these studies, men at highest risk of mortality despite treatment were noted to have an increase in PSA by 2.0 ng/mL the year before diagnosis. In the series from University of Toronto with the longest published median follow up of 15 years, PSA DT of <3 years was initially used to recommend intervention. This cut off was somewhat arbitrarily selected, as it seemed to result in a clinically acceptable treatment rate. Eventually this was abandoned as strict trigger for intervention, however, as it did not correlate with pathologic or more important predictive endpoints. PSA kinetics is currently considered unreliable as a sole trigger to prompt radical treatment (14). Iremashvili *et al.* reviewed PSA, PSA density, PSAV and PSA DT time in a cohort of 314 men on AS with surveillance biopsy performed at regular intervals (15). PSA metrics did not predict for progression until the 4th biopsy. The authors supported use of PSA kinetics in helping to define indication for repeat biopsy in men who have had regular biopsies for at least 3–4 years. Similar to the experiences from the University of Toronto, the PRIAS trial (16) formerly employed PSA DT <3 years as indication for radical therapy, but since 2009 their protocol was amended for changes in PSA to prompt further workup, including early repeat prostate biopsy. Novel biomarkers or advanced imaging will eventually clarify the role for PSA in following men on AS and may tailor surveillance strategies and timing of tests based on PSA changes.

The greatest clinical predictor of outcome for any man with CaP is GS. Surgical series with pure GS 6 CaP show no evidence of lymph node metastases suggesting that this is the most indolent lesion (17-19). Most protocols therefore utilize confirmatory and repeat biopsy to assess for GS changes over time as the most common trigger for intervention. Biopsy tissues changes in the form of GS upstage, or increasing core number or length are the most common indicator of disease progression and serve as most frequent trigger for intervention. Concerns over the long-term risks of multiple prostate biopsies along with interest in less invasive means of surveillance have prompted ongoing studies with novel imaging techniques and biomarkers for disease progression. Additionally, serial digital rectal exam and TRUS findings may identify disease upstaging (20,21).

Molecular markers

While biomarker assays are now commercially available to assess risk beyond pure clinical features and potentially assist in patient selection for AS, investigators are also studying novel biomarkers for surveillance of men with low risk CaP over time. PSA is a serine-protease produced and released by epithelial cells of the prostate gland. It is secreted as an inactive proenzyme (proPSA) into seminal fluid and subsequently activated by multiple enzymes produced by the prostate. Serum PSA itself occurs in several different molecular forms: free PSA (fPSA, composed of several subtypes, proPSA, cleaved PSA and others) and complexed PSA (22). Multiple studies support use of the PSA isoform proPSA as a predictor of significant CaP (23,24). The Prostate Health Index (PHI) combines PSA, fPSA and proPSA and has been shown to improve detection of CaP, particularly clinically significant disease (25). Heidegger *et al.* evaluated a multi-institutional cohort of men who were considered candidates for AS based on clinical criteria, with proPSA and PHI and found this improved detection of more aggressive disease and therefore may help in patient selection or disease monitoring (26).

The Four-Kallikrein Panel Tissue kallikrein and kallikrein-related enzymes are a family of 15 closely related serine proteases with high homology (27). A serum biomarker test known commercially as the 4Kscore® Test (OPKO Lab, Nashville, TN) incorporates a panel of four kallikrein protein biomarkers (total PSA, free PSA, intact PSA, and human kallikrein-related peptidase 2) and other clinical information in an algorithm that provides a percent risk for presence of high-grade (GS ≥7) cancer on biopsy. Amongst men suspected of having CaP, several studies have found that these markers improve prediction of high grade cancers compared to that of established risk calculator or models using tPSA alone (28,29). The Canary Prostate Active Surveillance Study (PASS) investigators evaluated the utility of 4K panel in predicting presence of high grade CaP in men with GS 6 disease on AS. Men were enrolled as part of a prospective, multi institutional study and the authors found that the 4K panel was significant associated with reclassification at first biopsy (30).

Other biopsy pathologic findings have been investigated as potential biomarkers in men with low risk disease. Serial prostate biopsy and impact on histologic inflammatory cell infiltrate has been described previously (31). The authors concluded that repeated biopsy in an AS population did not appear to be associated with degree of inflammatory cells.

Other investigators have evaluated the serum neutrophil to lymphocyte ratio as a marker of cancer-related inflammation. Gokce *et al.* (32) evaluated 210 prostatectomy specimens of men with clinical low risk disease who would have been candidates for AS and reported that serum neutrophil to lymphocyte ratio predicted upgrading at the time of RP as well as risk of biochemical recurrence after treatment.

Novel imaging

As previously discussed, there are many limitations to standard TRUS for monitoring men on AS and outside of very select centers (20,21) has limited value (33). The utility of multi-parametric MRI (mMRI) in the diagnosis and staging of CaP is rapidly expanding. Accurate identification of those with low risk disease as opposed to clinically significant disease at the time of diagnosis is key to the success and safety of surveillance as a viable treatment strategy. In a study by Ahmed *et al.* (34), results from the Prostate MRI Imaging Study (PROMIS) trial showed that mMRI when used as a screening tool in men with elevated PSA was more sensitive that TRUS biopsy for detection of clinically significant CaP. Multiparametric MRI demonstrated 88% sensitively (45% specificity) in detection of GS ≥ 3+4 disease.

As mMRI has been shown to primarily identify clinically significant CaP, this is an attractive potential, less invasive modality to follow patients enrolled in AS. In addition, mMRI/US fusion technology has facilitated target lesion biopsy to reduce sampling errors inherent with standard template prostate biopsy. Mullins *et al.* (35) retrospectively reviewed MRI findings of men on AS and compared with TRUS guided biopsy, and found that men with suspicious MRI lesions were more likely to be reclassified over time. Guo *et al.* (36) performed a meta-analysis on 7 studies from 2010–2013, studying the diagnostic accuracy of MRI on disease re-classification amongst AS candidates. They found a relatively low positive likelihood ratio of 3.1, high negative likelihood ratio (0.4), along with poor sensitively (0.69) and specificity (0.78). The authors questioned whether the evidence supports use of mMRI for disease reclassification.

Serial or surveillance mMRI is attractive as a less invasive means to monitor men over time, however has not been formally validated in AS cohorts. In a single AS series which included men meeting strict inclusion criteria (≤ T1c, GS ≤6, PSA density ≤0.15, no more than 2 cores or 50% disease in single core), 58 men were followed for 16 months (median) with mMRI and mMRI/US fusion biopsy (37). The authors found that one third (17/58) of men experienced evidence of disease progression on mMRI. Fifty-three percent of these men (9/17) demonstrated GS progression (3+3 to 3+4), resulting in predictive values of 53% and 80%, respectively (37). Habibian *et al.* (38) sought to describe mMRI characteristics of prostate cancers in patients who discontinue AS – specifically for concerns over tumor upgrading. Of 114 men on AS who had mMRI at enrollment and subsequent follow up, 14 (12.3%) discontinued surveillance due to concerning changes seen on MRI including extracapsular extension, new suspicious lesions or increasing size of a known lesion. Re-biopsy of these men found that nearly half had tumor upgrading. Felker *et al.* (39) described 49 men on AS with GS 6 disease who had mMRI on enrollment and again at 6 months of follow up. Overall, GS progression occurred in 39% of cohort. Ten men experienced MRI progression, 70% (7/10%) of which demonstrated pathological progression, yielding 90% specificity, 37% sensitivity for mMRI (39). Frye *et al.* (40) followed a cohort of men on AS, including those with 2 or more MRI-fusion guided biopsies (N=166). Targeted biopsy identified 44.9% of patients with progression as compared to 30.6% of men with systematic 12-core biopsy. Progression on mMRI was the sole predictor of pathologic progression during surveillance (P=0.013).

Multiparametric MRI may not be accessible in all centers and in has cost effectiveness implications that remain unanswered. Serial transrectal ultrasound (TRUS) findings in men enrolled in AS have been investigated. Investigators from the University of California San Francisco (20) evaluated the incidence, growth dynamics and clinical significant of changes in prostate lesions of men enrolled in their AS program. They were able to identify 39% of men with progression by TRUS findings including size, number of lesions and stage. TRUS progression was independently associated with biopsy progression. Additionally, investigators from the University of Southern California (21) found that within their AS population over an 11-year period, significant TRUS findings such as blood flow as measures by a Doppler grading scale were associated with pathological progression.

Intervention without clinical progression

Some degree of attrition in AS cohorts, unprompted by any clinical changes, is expected. A 2017 review (41) of prospective trials of AS for low risk CaP reported overall

5- and 10-year treatment free survival rates ranging from 48–76% and 27–63%. Several trials originated with stringent entry criteria, which partly explain such variability in the treatment free survival rates. In addition to eligibility criteria, follow-up strategies, and thresholds for intervention also contributed to decision for radical treatment (41). Sociodemographic factors including race, age, education level and comorbidities have been found to be associated with AS discontinuation (42-44). Kelly *et al.* (42) found that black men were more likely to switch to active treatment, which has been described in prior studies (44). Additionally, the authors found black men were less likely to undergo serial re-biopsy perhaps explaining the higher rates of eventual treatment. Loeb *et al.* (43) examined 5-year outcomes of men enrolled in National Prostate Cancer Register of Sweden. After 5 years, about two thirds of men remained on surveillance. Predictors of discontinuation were younger age, less comorbidity, and more education. One fifth of men discontinued due to "patient preference".

Conclusions

The oncologic safety of AS for appropriately selected men with CaP is well supported by early and intermediate outcomes described by large centers. With promising survival outcomes as well as avoided morbidity of radical treatment, this strategy should be offered to men with low risk disease. Key to the success of surveillance is accurate and timely monitoring for cancer progression. While traditionally this included PSA changes or DRE findings, the ever-growing number of available biologic molecular markers, is now revealing potentially greater ability to detect clinically significant disease. Additionally, the emergence of advanced MRI technology has shown improved detection of high-grade cancer in AS populations. Despite these advances, we face an ongoing dilemma as to how best to incorporate these novel technologies into a feasible, cost effective and efficacious monitoring strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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