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INVITED OPINION

Prostate Cancer

Active surveillance monitoring: the role of novel biomarkers and imaging

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"CANCER" is a disease state that leads to progressive illness that is uniformly fatal without treatment. Hippocrates invoked the Greek word *karkinos*, or "crab," to describe tumors he observed. For centuries, "CANCER" remained a disease that was recognized primarily in its locally advanced or metastatic stage, when it was almost uniformly fatal.

However, beginning in the late 20th Century medical advances in imaging and tumor markers have enabled us to detect cancerous cells when the disease is still confined to the organ of origin and amenable to cure. While at first glance, this would seem to be of great benefit to humankind, and in many diseases it has been, we have now come to recognize that not all cancerous appearing cells progress into the entity first described by Hippocrates, and that treatment may not improve survival or worse, may violate Hippocrate's first tenant; *primum*, *non noce* … first, do no harm.

The prototype disease state exemplifying this conflict between early detection and "CANCER" is prostate cancer where the over-whelming majority (97%) of men diagnosed with a prostate will NOT die of prostate cancer.

Active surveillance for such nonlethal prostate cancer has gained greater acceptance over the past decade by both physicians and patients. However, confounding the total success of this management strategy is the random nature in which blinded biopsies of the prostate gland are obtained and the multifocality of the disease itself. Because, thousands of men do die of prostate cancer each year, we remained concerned that we are understaging and therefore undertreating a more significant cancer than detected, or that the cancer progresses beyond curability while the patient is actively surveyed. In assessing 626 men who met the Prostate Cancer Research International Active Surveillance (PRIAS) criteria but underwent immediate radical prostatectomy, El Hajj *et al*. found that 20.6% were upstaged (≥ pT3), 44.9% upgraded (≥ Gleason 7), and 50% were reclassified to unfavorable prostate cancer.[1] In addition, when the John's Hopkins group updated their experience managing 769 patients with an active surveillance program, at 2-year into the program 19% had a prostate cancer intervention.[2] By 5- and 10-year into the program 41% and 59% had a prostate cancer intervention indicating that the majority of men may just be delaying treatment. Whether this delay in intervention negatively impacts their cancer-specific survival is not yet determined.

The success of any monitoring plan for men on active surveillance relies heavily on the ability to identify areas of previously undetected clinically significant prostate cancer along with prompt recognition of cancer progression. If meaningful changes are discovered in a timely fashion, treatment can be effectively initiated with a high likelihood of success without compromising long-term cancer-related outcomes. Ideally, monitoring would be noninvasive, infrequent, individualized and highly accurate in characterizing the cancer within the prostate. Practically, this is not currently feasible.

While there is no widely accepted standard-of-care for selection criteria or monitoring of men on active surveillance, most clinicians recommend clinic visits along with PSA and digital rectal examination every 3–6 months supplemented by a prostate biopsy every 1–3 years. If a man's medical status or life expectancy changes while on surveillance, the monitoring regimen is altered accordingly.

Obtaining a PSA while on active surveillance is routine, frequent, and intuitive. Unfortunately, absolute PSA level and PSA kinetics do not reliably predict prostate cancer progression events, metastases, or cancer-specific deaths. Among a large Scandinavian cohort of men on watchful waiting (a distinct entity from active surveillance which recommends treatment only if symptoms or metastases) for prostate cancer, neither baseline PSA nor PSA doubling time accurately predicted long-term risk of prostate cancer death.[3] Similarly, among 290 men on active surveillance at Johns Hopkins between 1994 and 2008, neither PSA velocity nor doubling time could reliably predict progression while on surveillance or pathologic findings in those ultimately proceeding with prostatectomy.[4] This reality is somewhat counterintuitive to patients and physicians, particularly since the over-whelming majority of these men were diagnosed with prostate cancer because of an elevated screening PSA. However, perhaps not surprisingly, men with low-volume and low-grade cancers often have elevated PSA levels due to noncancerous causes and even modest growth of their cancer is unlikely to appreciably alter the PSA. In addition, PSA levels can fluctuate and be dramatically different when measured over many years, even in men without prostate cancer.[5] For these reasons, men entering a surveillance program should be preemptively educated about the limitations and variability of PSA. While PSA should be routinely measured in men on surveillance, a significant rise should always prompt a recheck weeks or months later and rarely be the sole impetus for converting from surveillance to treatment.

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Table 1: Clinical prediction of Active Surveillance qualification for 133patients undergoing 3.0T MRI followed by radical prostatectomy. (From Turkbey B, *et al.*[18])

	Sensitivity (%)	*PPV (%)*	*Accuracy (%)*
D'Amico	93	25	70
Epstein	64	45	88
CAPRA	93	20	59
MP-MRI	93	57	92

MP-MRI: multiparametric magnetic resonance imaging; PPV: positive predict value; CAPRA: cancer of the prostate risk assessment score

There are many PSA isoforms, and recent research has evaluated their ability to predict progression while on active surveillance. In a large European cohort, baseline percent free PSA was independently associated with progression whereas PSA was not.[6] While encouraging, it is unknown whether serial percent free PSA measurements are clinically useful. Prostate health index (phi), a formula incorporating total PSA, percent free PSA, and pro-PSA when measured longitudinally has been shown to predict cancer progression on biopsy in men on active surveillance.[7] Although further research and larger studies are needed, particularly with the longitudinal evaluation of PSA isoforms, preliminary data suggest this approach is promising to more accurately identify men at risk of progression while on surveillance.

Urine and prostatic fluid have also been evaluated in this setting. Levels of PCA3 (prostate cancer antigen-3), a cancer-specific gene that expresses noncoding RNA expressed from the prostate following a rectal examination, were similar between men on surveillance experiencing progression and those without progression.[8] Even after controlling for other variables, PCA3 was not associated with progression. Among a cohort of 387 men, urinary measurement of PCA3 and TMPRSS2:ERG (androgen-dependent gene fusion) were associated with higher tumor volume and higher Gleason grade on repeat biopsy, but these observations were not maintained on multivariate analysis.[9] Based on currently available data, the use of urinary markers for monitoring men on active surveillance is not recommended outside of a clinical trial.

Multiple tissue-based markers have produced encouraging results. ERG expression on a diagnostic biopsy was associated with a 58% rate of progression within the first 2 years on active surveillance compared to 21% for those without ERG expression.[10] In addition, two novel and commercially available tissue-based markers (Prolaris and Oncotype Dx) are independently associated with adverse pathologic outcomes at prostatectomy. This finding was evident even among men with low-risk cancer characteristics at biopsy whom might otherwise have considered active surveillance.[11,12] It is possible, though currently unstudied, whether these tissue-based biomarker tests will eventually be helpful to either select for or monitor men on surveillance.

MRI is currently the best imaging tool available to characterize prostate cancer. MRI-guided transperineal biopsies, when compared with transperineal biopsy alone, identified 95% of clinically significant cancers (defined as maximum cancer length ≥4 mm and Gleason score ≥7) with far fewer biopsy cores required (median: 5 *vs* 30).[13] Among 60 men with low-risk prostate cancer undergoing restaging biopsy while considering active surveillance, MRI was strongly associated with upgrading (defined as Gleason ≥7, >3 cores, or >50% of a single core.[14] Rates of upgrading based on a normal MRI, suspicious lesion <1 cm, or suspicious lesion >1 cm were 9%, 25%, and 77%, respectively. A similar study at Memorial Sloan-Kettering reported the likelihood of upgrading at rebiopsy was directly associated with the likelihood of cancer as visualized on the MRI with an odds ratio ranging from 2.1 to 3.9 depending on the individual radiologist.[15] Lastly, but importantly, two separate studies have suggested lesions suspicious for cancer on baseline MRI are associated with higher rates of Gleason grade progression while on active surveillance.[16,17] To assure the safety and success of active surveillance, accurate and timely methods to detect previously unrecognized high-grade cancer or cancer progression are essential. Free PSA, prostate health index (phi), MRI, and biopsy-based tissue markers are promising methods that aim to improve upon current surveillance techniques. Larger and more detailed validation studies, along with investigation of novel methods, are necessary (**Table 1**).

EDITORIAL COMMENT – (BY DR. JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

The article by Drs. Ward and Eggener compliments the Babaian paper nicely in this special issue as they both outline the key dilemmas in active surveillance. With a focus on novel serum and urine markers, we can offer risk refinement to standard clinical features to assist with allocating the correct patients to surveillance versus treatment. As they also review, the multi-parametric MRI can behave like biomarkers in identifying higher risk populations for repeat biopsy. As the 2014 International Prostate Forum was structured, common clinic populations include men with prior negative biopsy and men on active surveillance. We know that a single random biopsy does not eliminate the risk of future cancer diagnosis or future high-grade cancer diagnosis. These emerging trends in biomarkers and imaging improve our ability to "resift" through these populations to pull out the true cancers at an earlier stage.

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