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 state 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 Hippocrates’s first tenant; primum non nocere... 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 Johns 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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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. 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. 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. 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. 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. 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. 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). 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). 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. 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. 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).

**REFERENCES**

1. El Hajj A, Ploussard G, de la Taille A, Allory Y, Vordos D, et al. Analysis of outcomes after radical prostatectomy in patients eligible for active surveillance. BJU Int 2013; 111: 53–9.

2. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JJ, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Urol Oncol 2011; 29: 2185–90.

3. Fall K, Garmo H, Andrén Ö, Bill-Axelson A, Adlafsson J, et al. Prostate-specific antigen levels as a predictor of lethal prostate cancer. J Natl Cancer Inst 2007; 99: 526–32.

4. Ross AE, Leeb S, Landis P, Partin AW, Epstein JJ, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Urol Oncol 2010; 28: 2810–6.

5. Eastham JA, Riedel E, Scardino PT, Shike M, Fleishner M, et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA 2003; 289: 2695–700.

6. van As NJ, Norman AR, Thomas K, Khoo VS, Thompson A, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008; 54: 1297–305.

7. Tosoian JJ, Leeb S, Feng Z, Isharwal S, Landis P, et al. Association of [−2]proPSA with biopsy reclassification during active surveillance for prostate cancer. J Urol 2012; 188: 1131–6.

8. Tosoian JJ, Leeb S, Kettermann A, Landis P, Elliot DJ, et al. Accuracy of PCA3 measurement in predicting short-term biopsy progression in an active surveillance program. J Urol 2010; 183: 534–8.

9. Lin DW, Newcomb LF, Brown EC, Brooks JD, Carroll PR, 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.

10. Berg KD, Vainer B, Thomsen FB, Rader MA, Gerds TA,
et al. 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.

11 Cooperberg MR, Simko JP, Cowan JE, Reid JE, Djaliilvand A, 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.

12 Klein EA, Cooperberg MR, Magi-Galluzzi C, Simko JP, Falzarano SM, 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.

13 Kasivisvanathan V, Dutour R, Moore CM, Ahmed HU, Abd-Alaeez M, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013; 189: 860–6.

14 Margel D, Yap SA, Lawrentschuk N, Klotz L, Haider M, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. *J Urol* 2012; 187: 1247–52.

15 Vargas HA, Akin O, Afq A, Goldman D, Zheng J, et al. Magnetic resonance imaging for predicting prostate biopsy findings in patients considered for active surveillance of clinically low risk prostate cancer. *J Urol* 2012; 188: 1732–8.

16 Fradet V, Kurehanewicz J, Cowan JE, Karl A, Coakley FV, et al. Prostate cancer managed with active surveillance: role of anatomic MR imaging and MR spectroscopic imaging. *Radiology* 2010; 256: 176–83.

17 Mullins JK, Bonekamp D, Landis P, Begum H, Partin AW, et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. *BJU Int* 2013; 111: 1037–45.

18 Turkbey B, Merino MJ, Gallardo EC, Shah V, Aras O, et al. Comparison of endorectal coil and nonendorectal coil T2W and diffusion-weighted MRI at 3 Tesla for localizing prostate cancer: correlation with whole-mount histopathology. *J Magn Reson Imaging*. 2014; 39: 1443–8.