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Is Active Surveillance Too Active?

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Abstract

Purpose of Review Many prostate cancer active surveillance protocols mandate serial monitoring at defined intervals, including but certainly not limited to serum PSA (often every 6 months), clinic visits, prostate multiparametric MRI, and repeat prostate biopsies. The purpose of this article is to evaluate whether current protocols result in excessive testing of patients on active surveillance.

Recent Findings Multiple studies have been published in the past several years evaluating the utility of multiparametric MRI, serum biomarkers, and serial prostate biopsy for men on active surveillance. While MRI and serum biomarkers have promise with risk stratification, no studies have demonstrated that periodic prostate biopsy can be safely omitted in active surveillance.

Summary Active surveillance for prostate cancer is too active for some men with seemingly low-risk cancer. The use of multiple prostate MRIs or additional biomarkers do not always add to the prediction of higher-grade disease on surveillance biopsy.

Keywords Prostate cancer · Active surveillance · Biomarkers · Prostate MRI

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy and second-leading cause of cancer death in men in the United States, with an estimated 268,490 diagnoses and 34,500 deaths expected in 2022 [1]. While prostate specific antigen (PSA)-based screening can lead to improved prostate cancer-specific survival, screening may also lead to overtreatment of low-risk prostate cancer. This is problematic because treatments with curative intent for this disease (i.e., radiation or radical surgery) have been associated with significant morbidity, including urinary incontinence, erectile dysfunction, and bladder/bowel irritation [2–4]. Furthermore, treatment for low-risk prostate cancer does not appear to change overall- or metastasis-free survival [5••, 6]. Given the lack of benefit and demonstrated potential harms for treating low-risk prostate cancer, the concept of active surveillance for prostate cancer was developed. Active surveillance entails a protocol-driven approach to managing men with very low-risk, low-risk, or low volume favorable intermediate risk prostate cancer, generally defined as

- Gleason grade group 1 with any number of cores involved or Gleason grade group 2 involving ≤3 cores
- Clinical stage T1–T2a
- PSA density < 0.15 or PSA < 10 ng/mL

When followed on prospectively-defined active surveillance protocols, men with lower risk prostate cancer who elect initial management with active surveillance have non-inferior prostate cancer-specific outcomes compared with men who elect initial treatment with surgery or radiation [7–11]. However, there is currently no universal protocol for active surveillance. Many of these protocols mandate serial monitoring at defined intervals, including but certainly not limited to serum PSA (often every 6 months), clinic visits, prostate multiparametric MRI, and repeat prostate biopsies. One of the hallmarks of active surveillance as opposed to a more passive watchful waiting strategy is serial prostate biopsy at defined intervals, regardless of serum PSA or prostate MRI findings.

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Current Guidelines and Protocols

Given the lack of benefit and potential for harm in treating lower risk prostate cancer with curative intent, multiple professional organizations have issued treatment guidelines recognizing active surveillance as the preferred initial management strategy for men with low-risk prostate cancer. These organizations include the American Urological Association [12••], European Association of Urology [13], the American Society of Clinical Oncology [14], and the National Comprehensive Cancer Network [15].

Current active surveillance protocols are listed in Table 1. There is a high degree of variability for recommended intervals between PSA testing, digital rectal examination, and repeat biopsy. For example, Johns Hopkins recommends repeat biopsy annually in men with low -risk prostate cancer [7], whereas the University of Toronto and many European centers recommend biopsy every 3–4 years after the first few biopsies [8, 16]. All protocols have been associated with very low rates of metastatic disease or death from prostate cancer.

Cost of Continued Surveillance

While active surveillance results in excellent clinical outcomes in terms of safety of cancer control and low morbidity, there are associated costs. These include direct financial costs of laboratory and imaging tests, advanced biomarkers, and physician clinic visits [17, 18] as well as indirect costs such as time away from work. Furthermore, diagnosis of prostate cancer and undergoing serial prostate biopsies incurs potential risks including post-biopsy infection [19] and psychological distress [20, 21•]. These represent ongoing costs and risks that patients will incur until they elect to discontinue surveillance or proceed with curative-intent treatment with radiation or surgery.

As there is potential for harm with the active components of active surveillance, it is worth asking, "Is active surveillance for prostate cancer too active?" What are the ideal observational interventions and time intervals to monitor low-risk prostate cancer while minimizing patient risk and costs? The following variables can be adjusted during active surveillance, which can result in more or less activity during active surveillance:

- Prostate biopsy
- Advanced imaging
- Serum and tissue biomarkers

Thus, performing too many of the above interventions could lead to overactive active surveillance. However, the desire for restraint must be balanced by the additional information gleaned from each intervention and how the results impact future interventions.

Outcomes on Surveillance Biopsy

Progression on active surveillance is defined as increase in prostate cancer grade and/or volume above predefined thresholds, often grade group 2–3 or >34–50% of biopsy cores containing cancer. Therefore, a surveillance prostate biopsy is a prerequisite for defining disease progression. As the goal of active surveillance is to identify prostate cancer at a still-curable state, and the only method to determine current pathologic state or upgrading is through prostate biopsy, serial prostate biopsies cannot be completely omitted in true active surveillance.

One key difference between active surveillance protocols is the time between biopsies. This can range from annually to once every 3–4 years (Table 1). Reported rates of freedom from prostate cancer-specific death include no reported cases (Johns Hopkins, Canary PASS) [7, 9], 2.8% at 10 years [8], and less than 1% [10]. Despite these excellent survival outcomes, all four of these studies report continued pathologic progression on

Table 1 Current active surveillance protocols

Institution/organization	PSA/physical exam	Repeat prostate biopsy
Johns Hopkins (7)	Every 6 months	Every 12 month for low risk Every 24 months for very low risk
UCSF (11)	Every 3 months	Every 12–24 months
University of Toronto (8)	Every 3 months × 2 years then every 6 months	At 6–12 months, then every 3–4 years
Canary PASS (9)	PSA every 3–6 months DRE every 6 months	At 6–12 months, at 2 years, then every 2 years
ASCO (14)	PSA every 3–6 months DRE every 12 months	At 6–12 months, then every 2–5 years
NCCN (15)	PSA no more than every 6 months DRE no more than every 12 months	No more than every 12 months

surveillance biopsy over time. There is no time horizon at which reclassification no longer occurs. To safely discontinue active surveillance, biopsy progression would need to follow an "ideal" Kaplan-Meier curve, with most reclassifications happening in the first few years, followed by a plateau where reclassification no longer happens (Fig. 1). As reclassifications continue to recur even years from diagnosis, it does not appear that discontinuation of surveillance biopsies is reasonable. However, greater spacing between biopsies, as demonstrated among men in the University of Toronto cohort, does not result in meaningfully worse outcomes. For this reason, an active surveillance protocol with biopsies every 3–4 years after the first 1–2 surveillance biopsies is likely to be active enough for many men.

Furthermore, the finding of no cancer on surveillance biopsy may have prognostic implications for future upgrading. Kearns et al. reviewed 657 from the Canary PASS study undergoing active surveillance for prostate cancer. Men with no cancer detected on the first surveillance (confirmatory) biopsy had a 50% decreased probability of future reclassification compared with men who had some cancer but no upgrading (HR 0.50, $p = 0.008$). Men with no cancer on second surveillance biopsy had an 85% lower chance of reclassification compared with those who had some cancer (HR 0.15, $p = 0.003$) [22]. Bloom and colleagues similarly reported on 542 patients on active surveillance, finding that a negative confirmatory MRI fusion biopsy was associated with a significantly decreased risk of future grade reclassification (HR 0.41, $p < 0.01$) [23]. Furthermore, Singh et al. also found a significantly lower rate of upgrading among 460 men with negative prostate biopsy while being followed on active surveillance for prostate cancer (HR 0.48, $p = 0.047$) [24]. Given that negative biopsy is common in these cohorts (20.5–32%) [22–24], using negative prostate biopsy to "de-escalate" the frequency of biopsies could be useful in the management of many prostate cancer patients on active surveillance.

MRI Findings

Prostate MRI has become a frequently-used adjunct to prostate biopsy in the management of men with low-risk prostate cancer on active surveillance. As MRI can be useful to identify areas of concern for high-grade prostate cancer, two key questions arise about its utility in active surveillance:

1. Can prostate MRI be used instead of surveillance biopsy?
2. Do serial MRIs improve detection of high-grade prostate cancer on active surveillance?

Liss and colleagues reviewed the MRI fusion prostate biopsy experience in the Canary PASS cohort. In a cohort of 361 men with 395 MRI studies and a median follow up of 4.1 years, they found that 108 (72%) of men were reclassified in terms of grade group. Of 194 fusion biopsies, grade group ≥2 cancer was found in only MRI-targeted cores 11% of the time and only in systematic cores 13% of the time [25]. Klotz et al. randomized 273 men with newly diagnosed grade group 1 prostate cancer to either systematic-only or MRI-targeted plus systematic prostate biopsy. They found that MRI targeting did not significantly increase detection of grade group ≥2 prostate cancer (27% versus 33%, $p = 0.3$), but MRI-only targeting would miss upgrading 7.9% of the time [26•]. Using the PRIAS study in Europe, Luiting and colleagues reviewed 1,185 patients who underwent 1,488 MRI fusion prostate biopsies and found no significant difference in upgrading between men who had prostate MRI prior to initial diagnosis and those who did not have MRI prior to initial diagnosis [27].

A recent meta-analysis by Rajwa and colleagues reviewed 15 studies including 2,240 men to evaluate serial prostate MRI for detection of prostate cancer progression during

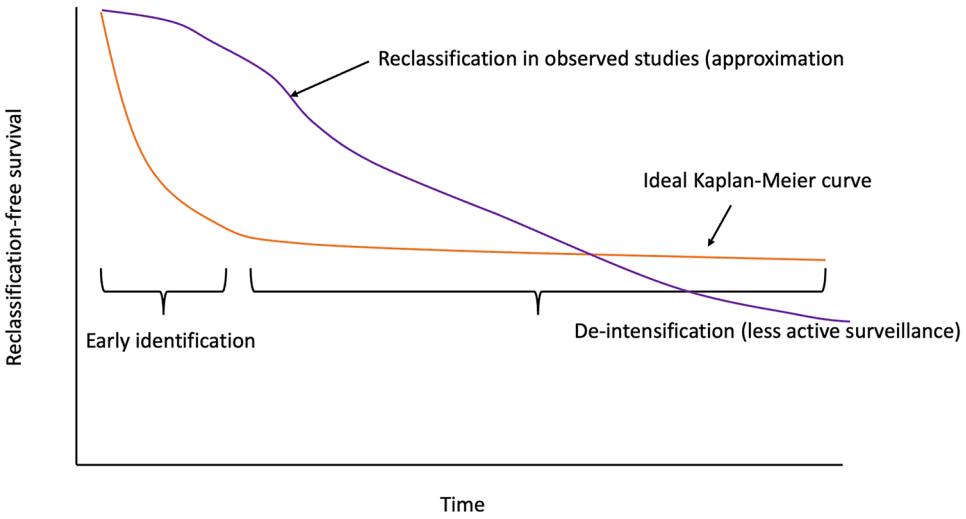

Fig. 1 Ideal and realistic Kaplan-Meier curves for reclassification

active surveillance. The negative predictive value for serial MRI was 0.81–0.88, leading the authors to conclude that serial MRI should not be used as the sole factor to exclude progression of prostate cancer on active surveillance [28]. Another systematic review by Hettiarachchi et al. analyzed seven studies including 800 patients to determine whether serial prostate MRI could adequately follow progression on active surveillance. The authors found that the negative predictive value for serial MRI to determine disease progression was 0.81, again leading to the conclusion that prostate MRI cannot replace MRI in the surveillance of men with low-risk prostate cancer [29].

The overall conclusion from these studies is that MRI cannot substitute for prostate biopsy during active surveillance. In fact, prostate MRI may not even significantly add to diagnostic accuracy of surveillance biopsy, once all other patient and disease factors have been accounted for. Both the American Society of Clinical Oncology [30] and American Urological Association [12] have issued statements that MRI should not be used in place of surveillance biopsy. In summary, the use of serial MRI in prostate cancer active surveillance may be "too active" and is a potential target for de-intensification.

Biomarkers

Prostate Specific Antigen

Another potential avenue for risk stratification in active surveillance for prostate cancer is serum and tissue biomarkers. Serial PSA measurement is a cornerstone of prostate cancer active surveillance, so understanding how PSA levels in men undergoing active surveillance are related to risk of progression is essential. The Johns Hopkins group evaluated 290 men with a median follow up of 2.9 years. Neither PSA velocity nor PSA doubling time was significantly associated with upgrading on surveillance biopsy [31]. Similarly, the group from University of California, San Francisco, reviewed 241 men on active surveillance with the finding that serum PSA does not significantly change in the first 24 months of active surveillance, which limits its utility in risk stratification in newly-diagnosed men [32]. Furthermore, the PRIAS group evaluated 5,302 men across 18 countries undergoing active surveillance for prostate cancer. They found that a PSA doubling time of less than 3 years did not predict for pathologic upgrading on surveillance biopsy compared with men who have longer PSA doubling times [33]. Cooperberg and colleagues from the Canary PASS cohort evaluated risk of progression among 851 men at 9 North American centers. They found that PSA kinetics significantly improved a linear mixed-effect model for predicting upgrading on active surveillance after adjusting for prostate size, time since diagnosis, biopsy findings, and diagnostic PSA [34]. When evaluating PSA density, Ediz et al. found that no man with a PSA density < 0.7 ng/mL/cc upgraded at a mean follow up of 38.1 months in 107 patients [35]. Thus, PSA is a useful adjunct for decision-making for men on active surveillance for prostate cancer, but it cannot be independently used to de-escalate surveillance biopsies.

Prostate Health Index and 4K Score

The Prostate Health Index (PHI) is a panel of three kallikreins, total PSA, free PSA, and [-2]proPSA, that has been approved by the FDA for prostate cancer diagnosis. Tosoian et al. evaluated 167 men on active surveillance with the finding that PHI improved prediction of upgrading on surveillance biopsy [36]. These findings were confirmed by Heidegger et al. in a multi-institutional cohort of 112 patients at four European centers [37]. Schwen and colleagues further found that a PHI <25.6 and PIRADSv2 ≤ 3 had a negative predictive value of 98% for grade reclassification [38].

A four kallikrein panel (4Kscore) has been developed to better predict prostate biopsy outcomes in men being screened for prostate cancer [39]. Investigators from the Canary PASS study, led by Lin, evaluated the utility of the 4Kscore in 718 men undergoing active surveillance for prostate cancer. They found that the 4Kscore did not improve prediction of upgrading on surveillance biopsy compared with a model accounting for PSA, biopsy characteristics, body mass index, and prostate volume [40].

PCA3

Ploussard and colleagues evaluated whether urine *PCA3* helped predict upgrading in 106 consecutive low-risk prostate cancer patients, with the finding the *PCA3* was associated with tumor size but not upgrading on surveillance biopsy [41]. Tosoian et al. found that urine *PCA3* improved prediction of grade reclassification on active surveillance when added to a multivariable model including age, risk classification, and PSA density [42]. Newcomb and colleagues evaluated with urinary TMPRSS2:ERG and *PCA3* were associated with upgrading in a cohort of 782 men. They found that urinary TMPRSS2:ERG was not associated with grade reclassification, but *PCA3* incrementally improved predication of prostate cancer upgrading [43].

Aging Out of Surveillance

The lifetime risk of death from prostate cancer decreases as men age, as the competing risks of death begin to outweigh the risk of death from prostate cancer. The natural history of low grade prostate cancer is favorable, with rates of lymph node metastases at prostatectomy estimated at 0.2% [44]. In the European Randomized Study of Screening for Prostate

Cancer, only 15 of 692 men (2.2%) diagnosed with Gleason 3 + 3 prostate cancer died from prostate cancer at a median follow up of 12.8 years [45]. When the biopsy pathology of these 12 men was re-evaluated using International Society of Urologic Pathology 2014 standards, 8/15 (53%) of these men were reclassified to Gleason 3 + 4. Thus, 10-year mortality from Gleason 3 + 3 prostate cancer is likely less than 1%. Given incredibly low risk of metastasis and death associated with Gleason 3 + 3 prostate cancer, it would be reasonable to stop all active surveillance in men with a life expectancy less than 10 years. Life expectancy can be estimated using readily-available online risk calculators, such as the United States Life Expectancy Calculator [46].

Personalized Treatment Plans for Active Surveillance

Personalized treatment plans can be made based upon available clinic-pathologic data in regard to biopsy pathology, biomarkers, and imaging. This data may be used to monitor patients at different intervals. For example, the following two men may be treated in active surveillance with significantly different biopsy intervals:

> Example 1: 67-year-old man with 2 positive cores of grade group 1 disease, no adverse tumor characteristics (i.e., no perineural invasion or cribriform pattern), a PHI value of 38 (relatively lower risk of disease re-categorization), and a negative prostate MRI.
> Example 2: 70-year-old man with 6 positive cores of grade group 1, perineural invasion, a PHI value of 68 (higher risk of disease re-categorization), and an MRI with a 1.5c PIRAD 4 lesion.

In the first example, the patient collectively has lower risk features and perhaps his biopsy schedule would be more appropriate at 4-year time points. However, the data presented in the second example creates an overall gestalt that is more aggressive. This patient may be better served by surveillance biopsies every 1–2 years.

Conclusions

In conclusion, active surveillance for prostate cancer is too active for some men with seemingly low-risk cancer. The use of multiple prostate MRIs or additional biomarkers do not always add to the prediction of higher-grade disease on surveillance biopsy. However, these adjuvant tools can be used collectively to better predict who may require more or less surveillance biopsies. Finally, completing risks of death will eventually outweigh the risks of prostate cancer metastasis and death in men who age out of prostate cancer active surveillance.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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- •• Of major importance

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