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# Overactive Surveillance: Is "Conservative" Management for Low-risk Prostate Cancer Too Aggressive?

***Stacy Loeb*** [a,b,*]

[a] *Department of Urology and Population Health, New York University, New York, NY, USA;* [b] *Manhattan Veterans Affairs Medical Center, New York, NY, USA*

Historically, most patients with low-risk prostate cancer underwent radical treatment. Watchful waiting was for men who were too old and sick to receive treatment. Active surveillance (AS) was initially considered investigational and was rarely used. In fact, patients had to sign informed consent to join the Sunnybrook AS program for the first 8 yr, and it was not until 2003 that it was offered as a standard management option [1]. However, from 2004 to 2006 only approximately 10% of US patients were managed with this approach.

In 2010, the use of conservative management began to significantly accelerate [2]. Nevertheless, at that time it was primarily viewed as a management approach for elderly men, and the distinction was often blurred between watchful waiting (observation without curative intent) and AS (monitoring with curative intent). The 2010 National Comprehensive Cancer Network (NCCN) guidelines recommended "active surveillance" for very low risk patients with life expectancy of <20 yr and low risk patients with life expectancy of <10 yr, and as an alternative to treatment for those with longer life expectancy. In 2011, the same guidance was provided regarding "active surveillance", with the qualification that repeat biopsies are not indicated after the age of 75 yr or for men with life expectancy of <10 yr. Starting in 2014, the NCCN guidelines instead recommended "observation" (ie, watchful waiting) for patients with very low risk or low risk and life expectancy of <10 yr, versus "active surveillance" for patients with longer life expectancy. Thus, both the terminology and the application of conservative management approaches have greatly evolved over the years.

After many years of limited use, AS is now generally accepted as a standard management option, supported by the publication of randomized trials (eg, ProtecT [3]) and long-term data from prospective AS programs [1,4]. There is now consensus across multiple guidelines that AS is the preferred approach for patients with low-risk disease. The critical question is no longer whether AS is safe, but rather how it should be implemented. The 2011 NCCN guidelines recommended repeat biopsy as often as every 12 mo, and some of the major AS programs incorporated annual repeat biopsies. These protocols were designed at a time when the outcomes of AS remained uncertain, and there was substantial concern about the extent of upfront misclassification from a ~12-core diagnostic biopsy. However, yearly repeat biopsies represent a substantial cumulative burden in terms of patient morbidity and cost to the health care system. Furthermore, times have changed with the advent of multiple testing options that can reduce the likelihood of misclassification, including magnetic resonance imaging (MRI)-targeted biopsies and genomic tests.

Several AS programs with different inclusion and follow-up protocols have reported 95–99% metastasis-free survival and 97–99% cancer-specific survival at 15 yr for low-risk disease [1,4]. Although randomized data are not available to directly compare the long-term outcomes between different approaches to AS, data from mathematical models suggest that annual biopsies are not necessary for most patients with low-risk prostate cancer, and that excessive testing may cause greater harm than benefit for older patients. For example, our group published a Markov model comparing different AS protocols over a lifetime horizon [5]. For a hypothetical cohort of men diagnosed with prostate cancer in their 50s, we found very little difference in quality-adjusted life years between annual biopsy until age 75 yr and annual MRI with biopsy only for suspicious

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* 227 E 30th Street, 6th floor #612, New York, NY,10016, USA
E-mail address: stacyloeb@gmail.com.

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findings, or even biopsy every 5 yr. Notably, for a cohort of men aged >65 yr at diagnosis, the model revealed a reduction in quality-adjusted life years with any AS protocol compared to watchful waiting. That is, on average we found a greater net harm than benefit for biopsy-based surveillance protocols for men aged >65 yr because the extremely limited gain in life expectancy was offset by a reduction in quality of life due to treatment-related side effects.

That notwithstanding, AS use is common for men aged >65 yr. In the largest global AS registry (Movember GAP3), 50% of the men were aged >65 yr at diagnosis [6]. At 5 yr of follow-up, <2% have converted to watchful waiting [7]. Population-based data also show ongoing use of surveillance biopsies among elderly men. As the use of AS continues to expand globally, it is time to re-examine the previous cutoff age of 75 yr for discontinuing biopsy-based surveillance and consider a lower threshold to reduce unnecessary harm from excessive testing. Because the ratio of benefits to harms is preference-sensitive, a shared decision-making process should be used in AS, similar to what is currently recommended for prostate cancer screening.

Overall, we urgently need a dynamic risk-adapted approach to AS, avoiding "overactive surveillance" for groups who are less likely to benefit (eg, older men and those with low-volume disease). Since reclassification is a conditional probability, it is also reasonable to reduce the frequency of biopsy for other patients with favorable results on longitudinal surveillance testing (eg, negative surveillance biopsies).

One possible approach, which is currently being explored in the Randomized Study of Active Monitoring in Sweden (SAMS), is to reduce the intensity of follow-up after extensive confirmatory biopsy [8]. From 2012 to 2016, 340 men from multiple Swedish centers were randomized to this approach versus a standard rebiopsy and follow-up strategy. In this issue of *European Urology*, Bratt et al. [8] report results from the initial confirmatory biopsies performed in this trial. Upgrading to Gleason grade group ≥2 was found in 16% versus 10% of these groups ($p = 0.09$). Additional follow-up is necessary to assess the primary endpoint of the trial, which is the proportion of men who receive active treatment at 5 yr. Although MRI and biomarkers were not included in SAMS, these represent alternative confirmatory testing options that could be used to verify upfront risk classification, and thereby potentially reduce the intensity of subsequent surveillance.

Recent data from Johns Hopkins showed that a combination of MRI plus the Prostate Health Index had a 98% negative predictive value for grade reclassification at the next surveillance biopsy, suggesting that noninvasive tests may be used to inform the frequency of biopsy during AS [9]. Even for settings in which markers and/or high-quality MRI are not readily available, several risk calculators have been created using longitudinal clinical data to predict the likelihood of subsequent biopsy reclassification [10]. Further studies are needed to examine the long-term outcomes of these alternative approaches to risk-adapted AS.

Overall, there has been significant progress in the field, with rapid acceleration in the uptake of AS globally. In fact, the US Preventive Services Task Force recently cited this as a primary reason for reversing their prostate-specific antigen screening recommendations from grade D (against screening) to grade C (shared decision-making). As an increasing number of men are pursuing this option in an effort to reduce overtreatment and its associated risks, our next challenge is to ensure that the AS protocol itself does not impose undue patient morbidity and that transitions to watchful waiting occur when appropriate.

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## References

[1] Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272–7.
[2] Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990–2013. JAMA 2015;314:80–2.
[3] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415–24.
[4] Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33:3379–85.
[5] Loeb S, Zhou Q, Siebert U, et al. Active surveillance versus watchful waiting for localized prostate cancer: a model to inform decisions. Eur Urol 2017;72:899–907.
[6] Bruinsma SM, Zhang L, Roobol MJ, et al. The Movember Foundation's GAP3 cohort: a profile of the largest global prostate cancer active surveillance database to date. BJU Int 2018;121:737–44.
[7] Van Hemelrijck M, Ji X, Helleman J, et al. Reasons for discontinuing active surveillance: assessment of 21 centres in 12 countries in the Movember GAP3 consortium. Eur Urol 2019;75:523–31.
[8] Bratt O, Holmberg E, Andren O, et al. The value of an extensive transrectal repeat biopsy with anterior sampling in men on active surveillance for low-risk prostate cancer: a comparison from the Randomised Study of Active Monitoring in Sweden (SAMS). Eur Urol 2019;76:461–6.
[9] Schwen ZR, Mamawala M, Tosoian J, et al. Prostate Health Index and multiparametric magnetic resonance imaging to predict prostate cancer grade reclassification in active surveillance. J Urol Suppl 2018;188:e144.
[10] Ankerst DP, Xia J, Thompson Jr IM, et al. Precision medicine in active surveillance for prostate cancer: development of the Canary-Early Detection Research Network active surveillance biopsy risk calculator. Eur Urol 2015;68:1083–8.