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Active Surveillance: Very Much "Preferred" for Low-Risk Prostate Cancer

THE 2022 National Comprehensive Cancer Network® (NCCN®) prostate cancer guideline was recently released and features many commendable updates. However, one important revision was introduced: for men with low-risk disease, active surveillance (AS) is no longer considered "preferred," but rather is presented as an option alongside surgery and radiation therapy.

The "preferred" designation was introduced in the 2019 NCCN guideline, concordant with the AUA and European Association of Urology guidelines, which have recommended AS as the preferred management since 2018[1] and 2020,[2] respectively. Consequently, for the past 2 years, clinicians have been able to inform patients, primary care providers and policymakers skeptical of early detection efforts that all major guidelines support AS as the preferred standard of care for low-risk prostate cancer. Persistent and pervasive overtreatment of low-risk disease was and remains a major public health concern, in addition to a major driver of the 2012 U.S. Preventive Service Task Force "D" recommendation against all prostate specific antigen-based screening. An increase in the appropriate use of AS was explicitly cited as a major factor prompting the 2018 upgrade to a "C" recommendation favoring shared decision making.[3]

Our interpretation is "preferred" never implied AS as the only option for men with low-risk disease. Individual circumstances—very high-volume disease in a young patient, extensive family history of lethal prostate cancer, adverse genomic or imaging results, extreme patient anxiety or inability to adhere to routine surveillance—may properly lead a man to elect immediate treatment. "Preferred" denoted, rather, that the default recommendation for most men with low-risk disease should be AS. Actively removing the designation suggests new data have led to the alteration; however, no such data exist to our knowledge.

Evidence strongly supports the assertion that pure Grade Group 1 cancer (characteristic of all low-risk prostate cancer) never extends to adjacent organs, metastasizes or causes symptoms,[4] leading many groups to question whether it should even be called cancer.[5] Multiple large international series of low-risk cancers have shown AS to be safe, with an extremely low long-term likelihood of metastases or death.[6–9] Importantly, these large cohort studies collectively have been comprised of men across the spectrum of favorable-risk prostate cancer, not exclusively those with "very low-risk" disease, but rather include a substantial proportion of men with low and occasionally even favorable-intermediate-risk prostate cancer.

Abbreviations and Acronyms
AS = active surveillance
NCCN® = National Comprehensive Cancer Network®

Nationally, we have made tremendous progress in improving rates of AS for low-risk disease, which have risen from around 10% to about 50% over a 10 to 15-year span.[10,11] However, we still lag behind most other countries and have significant work to do. While there is no established "optimal" rate of AS for low-risk disease, the 80% rate achieved in, for example, Sweden[12] and in the U.S. Veterans Affairs health system[13] seems a reasonable goal. Zooming in reveals profound variations in care. At the level of the individual urologist, urology practice and even county, rates of surveillance range from 0% to 100%.[11,14] Recognizing that rates of AS remain too low and variation too high, both the AUA and the Michigan Urological Surgical Improvement Collaborative (MUSIC) have adopted the rate of AS for low-risk (not limited to very low-risk) prostate cancer as a quality measure in their Centers for Medicare and Medicaid Services-endorsed quality registries. Removing the "preferred" designation from national guidelines may harm these efforts to decrease the utilization of low value prostate cancer care.

Certainly, it is important to highlight the biological heterogeneity within the low-risk category, and these patients can be substratified effectively and consistently using a number of well-validated,

0022-5347/22/2072-0262/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000002341
Vol. 207, 262-264, February 2022
Printed in U.S.A.

linear risk prediction systems. We can refine prognostic estimates still further with imaging and other biomarkers, but these are not necessary in all or even most low-risk cancers. The commonly utilized "very low-risk" designation sets an exceedingly low threshold for disease risk, and substantial data indicate it is far too conservative in defining biological and clinical indolence. In an era in which a growing number of cancers are detected via magnetic resonance imaging-guided biopsies, with explicit oversampling of visible lesions, the use of core volume thresholds is losing what relevance it once had. More importantly, we should remain cognizant of 2 large randomized controlled trials (SPCG-4 and PIVOT) comparing immediate treatment to watchful waiting (far less intensive than contemporary AS), both showing no benefit for treatment of low-risk cancer.[15,16] Modern patients undergo more thorough and better targeted biopsies, and low-grade cancer now includes a more restrictive pathological definition, leading to Gleason upgrading over time, both of which should lead to an even lower likelihood of benefiting from treatment. While both trials have their well-recognized limitations, taken together with the long-term followup from AS cohorts, they seem more than sufficient to support AS as the preferred management approach for most men with low-risk disease.

The goal of prostate cancer screening is to identify cancers that may one day impact a man's quality or quantity of life. Routine treatment of low-risk prostate cancer can significantly impact quality of life without any demonstrable benefit to quantity of life. What, then, should be our path forward for low-risk prostate cancer? A relatively small fraction (likely $<10\%-20\%$) of men with low-risk prostate cancer should consider treatment. Not only should routine clinical parameters be more consistently used for shared decision making, but we also have the benefit of time to allow for further assessment. Over the course of AS, assessments may include magnetic resonance imaging, genomic testing and/or repeat biopsy, as indicated, to ensure the safety and appropriateness of continued surveillance. The window of opportunity for cure is generally measured in years and decades, with curative treatment considered and usually achievable if a man progresses out of favorable-risk disease.

We feel strongly that extensive data and experience support the continued and strengthened endorsement of surveillance as "preferred." While AS may not be suitable for every patient, it is the right choice for the large majority of men with low-risk prostate cancer.

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