



Platinum Priority – Editorial

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Active Surveillance for Prostate Cancer: Barriers to Widespread Adoption

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Prostate cancer (PCa) represents a significant societal burden, accounting for substantial morbidity and mortality in men with an annual worldwide incidence of about 1 million cases and about 250 000 deaths [1]. The introduction of screening prostate-specific antigen (PSA) level has resulted in a stage migration whereby the majority of screen-detected tumors are small, low-grade, organ-confined lesions, which generally have a protracted natural history and limited cancer-specific mortality. Most men diagnosed with screen-detected PCa are likely to die with, rather than from, PCa. This has been shown in both the European and American screening trials and validates concerns related to PSA-induced overdiagnosis and overtreatment of potentially indolent cancers. While high-level evidence exists to support radical prostatectomy over watchful waiting in selected young men with clinically detected PCa [2], radical prostatectomy in that setting is associated with moderate overtreatment (the number needed to treat to prevent one PCa death ranges from 7 to 15) and potentially prolonged side effects [3]. A more recent trial, performed in US Department of Veterans Affairs hospitals, of radical prostatectomy for predominately screen-detected cancers has shown no mortality benefit for surgery over observation [4]. Despite these findings, a considerable majority of men in the United States and Europe who are diagnosed with screen-detected localized tumors receive aggressive treatment [5,6].

In the face of these considerations, active surveillance (AS) of PSA-detected tumors with delayed curative intervention at the time of disease progression or at the discretion of the patient should be considered as an acceptable management option [7]. The excellent systematic review by Dall'Era et al. [8] in this issue of *European Urology* comprehensively

summarizes the existing literature describing AS and highlights key issues that remain to be addressed.

Current criteria for AS used by most clinicians include men with low-risk tumors defined by clinical and biopsy pathology features. Most of the series highlighted by Dall'Era et al. include patients with clinical $\leq T2a$ tumors and serum PSA values ≤ 10 ng/ml [8]. Biopsy criteria generally included only men with Gleason score 3 + 3 or lower in no more than two or three cores positive for malignancy. These criteria are also in keeping with those described in the US National Institutes of Health State-of-the-Science Statement on AS [7]. Importantly, as highlighted by Dall'Era and colleagues [8], optimal or potentially more inclusive selection criteria for AS remain to be defined. While more conservative biopsy criteria may yield a patient population at lower risk for subsequent progression, such an approach will limit the number of men managed with this strategy and have little effect on overtreatment rates. Alternatively, inclusion of men whose tumors are larger or contain a small amount of Gleason 4 disease may be associated with more frequent and earlier conversion to aggressive therapy.

Additional potential barriers to the wider adoption of AS in low-risk PCa include concerns regarding disease misclassification in 30–50% of men [9] based on common clinical and biopsy criteria. Traditional transrectal ultrasound-guided biopsy of the prostate is fraught with inadequate sampling of the tumor, thereby leading to inaccurate grading and estimation of tumor volume, which can undermine physician and patient confidence in prostate biopsy results. As highlighted by Dall'Era et al., repeat, possibly extended, preferably template- or image-guided

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confirmatory biopsy should be considered to prevent undergrading [8]. Additional tools available to the clinician that may decrease disease misclassification include three-dimensional template-guided biopsy [10], which can provide more accurate detection of cancer and more accurate grade assignment. Additionally, multiparametric magnetic resonance imaging (MRI) of the prostate may have a role in guiding patient selection for surveillance both as a means to guide targeted biopsies into suspicious areas of the prostate and potentially monitor tumor volume noninvasively. It may also be possible to predict Gleason score from information gleaned from multiparametric MRI [11]. Molecular genetics will also likely allow clinicians to more selectively apply AS to individuals based on more accurate risk stratification, thereby increasing use of AS.

Patient and family anxiety is also a potential barrier to acceptance of AS. Beyond the initial concerns associated with a diagnosis of cancer, which can increase the short-term risk of cardiovascular events, patients electing to proceed with AS must deal with the additional unease stemming from uncertainty about the future and the risks of multiple future biopsies. Some patients or their family members may find the idea of *doing nothing* for their cancers inconceivable. Theoretically, adequate patient education and reassurance about the favorable risk profile of screen-detected cancers can alleviate much of the worry associated with a PCa diagnosis and AS. However, notwithstanding excellent outcomes with disease-specific and overall survival with AS, many younger patients justifiably wonder how applicable these results are to their long life expectancy and the occasionally unpredictable course of low-risk PCa. One suggestion to help allay patient concerns associated with the diagnosis of low-risk PCas is to avoid the term *cancer* in favor of something like *indolent lesion of epithelial origin*. This approach, however, remains controversial.

Another potential strategy to reduce patients' anxiety related to doing nothing while on AS is to consider adjunctive therapies. Results from the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) Trial support the concept that dutasteride therapy may decrease patient anxiety and delay both pathologic and therapeutic progression [12]. Another plausible strategy may be to focally ablate the patient's known cancer in situ. Patients may be reassured that something is being done to destroy the tumor that is known to be present and that such destruction may be associated with lower disease progression rates in the future in comparison to no treatment.

At this time, it is clear that AS is associated with acceptable disease-specific and overall mortality in the short to intermediate term. However, there are a number of questions surrounding AS that need to be addressed. Currently, the optimal selection criteria with which to appropriately identify patients best managed with AS and exclude those likely to progress remain to be defined. Additional work needs to be done in refining the ideal

surveillance regimen and prostate biopsy frequency, especially in light of increasing concerns related to biopsy-associated complications. It also remains to be seen how advances in biopsy techniques, imaging, molecular genetics, and biomarkers can be incorporated into AS regimens. Prospective studies such as the Canary Prostate Active Surveillance Study and the Prostate Testing for Cancer and Treatment trial are addressing some of these outstanding questions and hopefully will lead to more appropriate and widespread use of AS.

Conflicts of interest: Dr. Andriole has been affiliated with Amarex LLC, Amgen, Augmenix, Bayer, Bristol Myers Squibb Co., Cambridge Endo, Caris, Envisioneering Medical, GlaxoSmithKline, Janssen Biotech, Inc., Johnson & Johnson, Medivation, Myriad Genetics, Steba Biotech, Ortho-Clinical Diagnostics, Viking Medical, and Willex.

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