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European Association of Urology

Position Paper

Active Surveillance for Low-risk Prostate Cancer: The European Association of Urology Position in 2018

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Abstract

Active surveillance (AS) represents a well-recognized management option for many patients with low- and very low-risk prostate cancer (PCa). AS aims to reduce overtreatment whilst ensuring curative treatment for those in whom it is needed, without losing the window of curability. While long-term series have confirmed the safety of AS in carefully selected patients, this has resulted in new clinical questions. Can the inclusion criteria be expanded? Is there a role for biomarkers and multiparametric magnetic resonance imaging at diagnosis or during AS? What is the optimal follow-up schedule as well as the most meaningful trigger for definitive treatment? These questions, together with increasingly adopted heterogeneous protocols in AS, have prompted the European Association of Urology to produce a position paper corroborated by a summary of the scientific background on AS.

Patient summary: Active surveillance (AS) is becoming a widely adopted strategy for patients affected by low-risk prostate cancer. While a formal systematic review on the topic will soon be available, the European Association of Urology has produced specific statements for different open questions on AS.

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1. Introduction

Approximately 45% of men with screening-detected localized prostate cancer (PCa) are candidates for deferred treatment [1]. The Cluster Randomized Trial of PSA Testing for Prostate Cancer showed that a single PSA screening intervention increased the detection of low-risk PCa [2]. In this context, active surveillance (AS) represents a well-recognized option for the initial management of selected patients with low- and very low-risk PCa. This approach is increasingly used in this setting [3,4], with the aims of reducing possible overtreatment and achieving curative treatment for those with progressive disease without losing the window of curability [5]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening but still curable disease in men with adequate life expectancy. Current data supporting the role of AS are derived from ongoing prospective or retrospective cohorts. No formal randomized controlled trial is available comparing AS to standard treatment, although a randomized study of less intensive active monitoring showed no difference in overall

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survival (OS) at 10 yr when compared to active treatment mainly in men with low- and intermediate-risk PCa [6]. The largest published AS cohort coupled with the longest follow-up included 993 patients with low- or intermediate-risk PCa [7]. This prospective cohort enrolled men with clinical stage T1 or T2a and PSA ≤10 ng/ml, age ≤70 yr, and a Gleason score ≤6 or age >70 yr with a Gleason score of ≤3 + 4. Interestingly, men with intermediate-risk disease represented approximately 20% of the entire cohort of study. Moreover, neither multiparametric magnetic resonance imaging (mp-MRI; not available at the time of study initiation) nor extensive biopsy sampling were considered in the study. After a median follow-up of 6.4 yr, the 10- and 15-yr OS were 80% and 62%, respectively, and cancer-specific survival (CSS) rates were 98.1% and 94.3%, respectively. Radical treatment was received by 27% of this population, prompted by a PSA doubling time <3 yr (43.5%), a Gleason score progression on repeat biopsies (35%), and patient preference (6%). Thirty men (3%) developed metastases during follow-up: 2% of those initially classified as Gleason 6 as compared to 9.7% if initially Gleason 7 [8]. Several other protocols have investigated AS in organ-confined disease [9], including the PRIAS study which represents the largest prospectively enrolled cohort of men initially managed with AS [10]. Although a decline in adherence has been observed in real life [11], AS showed to be safe and able to reduce the extent of overtreatment in low-risk PCa, provided accurate patient selection. Given such favorable outcomes, several studies focused on how to expand indications and to increase adherence to AS protocols [12,13]. This has contributed to an increasing number of studies and recommendations [14,15], sometimes based on single institution expertise rather than on strong, large evidence. In particular, the role of imaging and biomarkers during AS is not yet standardized and different protocols have been implemented with these approaches at different stages of AS. Some studies used mp-MRI to confirm eligibility for AS [16,17], others included imaging to expand inclusion criteria for AS and to reduce misclassification by using fusion biopsies [18,19], or even to replace the key role of prostate biopsy during follow-up [20]. In addition to such recent implementations, there are still considerable variations among studies regarding patient selection, follow-up schedule, the use of confirmatory or repeat biopsy and what should trigger active treatment. Moreover, existing guidelines regarding AS for PCa vary widely [21]. These differences not only make comparison between these studies difficult but also contribute to highly heterogeneous protocols for AS, which is confusing to both physicians and patients. All these reasons have prompted the European Association of Urology (EAU) to produce a position paper on AS, as done previously for other topics [22–24].

2. Selection criteria for AS

2.1. Statement

Include all men with low-risk PCa for AS using a standardized prospective protocol. Men with longer life expectancy (ie, >20 yr) should be properly counseled about the lack of very long-term data of AS.

2.2. Scientific background

There are several long-term prospective AS cohorts that have been reported, with different inclusion criteria and different protocols [25–29]. These different selection criteria included men fit for curative treatment and a life expectancy of at least 10 yr with low/very low-risk disease defined on a combination of PSA, clinical stage, and number of positive cores (Table 1). Stricter criteria are better at defining clinically insignificant disease but exclude many men with indolent cancer. Less stringent criteria (ie, enrolment of men with low-risk PCa regardless of the extent of cancer at biopsy) also resulted in excellent CSS outcomes.

The two largest and most mature prospective AS cohorts include men with low-risk PCa managed at Sunnybrook Health Sciences Centre and Johns Hopkins University [7,30]. Data from the Hopkin's series showed that only two low-risk men (0.15%) died from PCa at 15 yr, whilst 30% of men died from competing causes [30]. Similarly, in the Canadian prospective cohort, the 10-yr overall CSS rate was 98% [7]. In both series, the number of cores involved with cancer and the greatest percentage of cores involved at first biopsy were significant predictors of both PCa reclassification to higher grade and increased tumor extent at re-biopsy. However, they were not associated with disease progression over time. These results match historical data derived from men receiving nonstandardized conservative management of low-risk PCa where the rate of 10-yr CSS was 92% [31].

Data from the ProtecT trial are also supportive of a favorable outcome of conservatively managed patients with localized disease. In the study by Hamdy et al [6], low- and intermediate-risk men initially managed with active monitoring did not show any increased risk of cancer-specific death compared with men randomized to active treatment. Interestingly, such outcomes were reached using a less stringent follow-up when compared to current AS protocols.

Similar results have been reported by the PIVOT trial, even though with significantly higher rates of overall mortality at 10 yr mainly due to poor patient selection [32]. Taken together, this data supports the indication to expand AS to all men with low-risk disease, regardless of the extent of PCa at initial biopsy. Moreover, the recent introduction of mp-MRI may also add value in correctly expanding indications of AS to all low-risk men. Initial negative mp-MRI at the time of AS initiation has been indeed shown to reduce the number of misclassified cancers [33]. Low-risk men with negative mp-MRI may have indeed favorable outcome on AS, regardless of the extent of low-grade cancer at biopsy [20,34,35]. Moreover, in case of a positive mp-MRI, the number of positive cores may lose its possible prognostic effect on the rate of misclassification. Several positive cores detected at the level

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