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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 over-treatment 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

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 $\leq 3 + 4$. 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

Table 1 – Active surveillance inclusion criteria

Criteria	Date of initiation	Note	T stage	Gleason score	PSA threshold (ng/ml)	No. of cores	PSAD	Core involvement (%)
<i>Goteborg (Godtman Eur Urol 2016)</i>	Jan 1995	AS was defined as no treatment within 6 mo from diagnosis. The most common reason for choosing AS was presumed low-risk PCa, but deferring treatment could also be due to comorbidities or patient preference.						
<i>John Hopkins (Tosoian JCO 2015)</i>	Jan 1995	very low-risk older patients	T1c ≤T2a	≤6 ≤6	– 10	Max 2 –	<0.15 –	<50 –
<i>Miami (Soloway Eur Urol 2010)</i>	Feb 1992		T1 – T2	≤6	15	Max 2	–	<20
<i>MSKCC (Adamy J Urol 2011)</i>	Sep 1997		T1 – T2a	≤6	10	Max 3	–	<50
<i>PRIAS</i>	2006		≤T2c	≤6	10	Max 2	<0.20	–
<i>(Bokhorst Eur Urol 2016)</i>	2012	if aged ≥70 yr	≤T2c	≤3 + 4	10	Max 2	<0.20	<10
	2015	More than two cores can be positive if an MRI, including targeted biopsies, is done at inclusion – If saturation biopsies are done (20 cores), 15% of cores can be positive with a maximum of 4	≤T2c	≤6	10	–	<0.20	–
<i>Royal Marsden (Selvadurai Eur Urol 2013)</i>	Mar 2002	Overall if aged >65 yr	T1 – T2	≤6 ≤3 + 4	15	<50% cores	–	–
<i>Sunnybrook (Klotz JCO 2015)</i>	From Nov 1995 to Dec 1999	– All low-risk – Age >70 yr	–	≤6 ≤3 + 4	10 15	–	–	–
	From Jan 2000	– All low-risk – Favorable intermediate-risk with life expectancy <10 yr	–	≤6 ≤3 + 4	10 20	–	–	–
<i>UCSF (Welty J Urol 2015)</i>	1990		T1 – T2a	≤6	10	<33% cores	–	<50

AS = active surveillance; MRI = magnetic resonance imaging; PCa = prostate cancer; PSAD = prostate-specific antigen doubling time.

of the same prostate lesion targeted by mp-MRI-guided biopsies may not be indicative of higher rates of cancer progression at subsequent biopsy. Therefore, patients may be diagnosed with several positive cores taken from the index lesion (IL) but still have good outcomes on AS.

For all these reasons, patients fulfilling low-risk criteria should be counseled about AS as initial management of PCa highlighting pros and cons of this approach as compared to active treatment. Patients should be aware of the lack of prospective randomized evidence comparing formal AS with any curative treatment but should also be re-assured about the excellent outcome of AS and the absence of solid evidence supporting any negative oncological effect in delaying active treatment in this patient group [7,30]. However, patients should also be aware of the lack of prospective data on the outcome of AS beyond 15–20 yr from diagnosis. Therefore, men with longer life expectancy should be properly counseled about the lack of very long-term data of AS. By contrast, young patients with long life expectancy may be those who have more to gain from delaying radical therapy for many years. Therefore, after proper counseling, they could still be initially managed with AS-provided accurate biopsy. This is due to the association between the number of cores taken and the risk of biopsy reclassification [36]. Such recommendations

may change when very long-term data of AS become available.

3. The role of pathologist and the need for pathological review

3.1. Statement

Report the number of cores submitted for pathological assessment and the number of positive cores per side. Report the linear percentage or length (in mm) of involvement by carcinoma in the single core with the greatest amount of tumor. Finally, consider central pathological review of biopsy specimens when commencing long-term conservative treatments.

3.2. Scientific background

Accurate histopathologic assessment at biopsy is crucial for the selection of men suitable for AS. According to a recent consensus meeting, the pathologic factors to be considered include Gleason grade, tumor extent measurements, histologic subtype of carcinoma, presence of perineural invasion, and involvement of peri-prostatic fat [37]. In particular, pathological variants that should likely exclude a man from

AS include prostatic adenocarcinoma with predominant ductal carcinoma histology (including pure intraductal carcinoma with the exception of high-grade prostatic intraepithelial neoplasia-like ductal adenocarcinoma), sarcomatoid and small cell carcinoma, as well as cribriform pattern.

Moreover, several detailed information should be given at initial biopsy, including the number and the fraction of positive cores, the linear percentage of carcinoma in each site (core), the linear percentage of carcinoma in the core with greatest amount of tumor, the overall linear percentage of carcinoma across all sites (cores), the linear millimeters of carcinoma in each site (cores), the linear millimeters of carcinoma in the core with greatest amount of tumor, and the total linear millimeters of carcinoma across all sites (cores). Although the role of some of these measurements is still unclear in terms of patient outcome on AS, accurate biopsy assessment is important to decrease the rates of PCa misclassification and to improve patient counseling. Indeed, some of these measurements are strictly related to misclassification although their impact on AS outcomes in terms of cancer control is still unknown.

Moreover, the role of these measurements not only at initial biopsy but also at confirmatory/follow-up biopsy is still unclear. In addition, it is yet to be determined whether such extensive assessment maintains prognostic significance also at targeted biopsies, given the increased ability to better target possible foci of PCa under MRI guidance. Therefore, although detailed biopsy characteristics are useful for improved PCa risk assessment, their role on long-term hard clinical endpoint in men with low-risk disease is still to be elucidated. Finally, although no solid evidence supports the role of second-opinion pathology on the re-assessment of prostate biopsies, it may be useful for an accurate selection of patients on AS, especially commencing long-term conservative treatments [38].

4. Use and timing of MRI in active surveillance

mp-MRI can be used to detect clinically significant PCa in men on AS in order to improve patient selection and to optimize cancer diagnosis and timing for intervention. This can be done in three settings during AS:

1. mp-MRI at the time of initial diagnosis.
2. mp-MRI before confirmatory biopsy.
3. mp-MRI during follow-up.

4.1. mp-MRI at the time of initial diagnosis

4.1.1. Statement

In patients without mp-MRI prior to initial biopsy who are diagnosed with low-risk PCa suitable for AS, mp-MRI is recommended to rule out significant PCa missed by the initial biopsy. In men diagnosed with low-risk PCa after mp-MRI, all the aforementioned inclusion criteria apply. In case of initial biopsy done under guidance of mp-MRI, both targeted and systematic biopsies are recommended.

4.1.2. Scientific background

Interest in the role of mp-MRI in the diagnosis of PCa was heightened following the publication of the PROMIS [39] and PRECISION study [40]. The PROMIS study suggested that mp-MRI might be able to avoid under grading in 18% of cases whilst avoid one in four biopsies. However, concerns about the reproducibility of this data have prevented a firm recommendation for pre-biopsy MRI. Recently, the first large, prospective randomized trial (PRECISION study) supporting the role of pre-first biopsy mp-MRI in reducing the number of low risk PCa detected while increasing the diagnosis of clinically significant disease has been published [40]. If additional evidence will support the role of triage mp-MRI, the number of low-risk men suitable for AS will inevitably decrease and new AS protocols for mp-MRI-detected intermediate-risk PCa will be likely available in the future. Recently, the role of mp-MRI for patients enrolled in AS has been addressed by a systematic review [33]. A lesion on MRI suspicious for PCa (namely, positive MRI) is seen in two-thirds of men otherwise suitable for AS. A positive MRI makes the identification of clinically significant disease at repeat biopsy more likely, especially when biopsies are targeted to suspicious MRI lesions [41]. Moreover, radical prostatectomy data showed that a positive MRI is more likely to be associated with upgrading (Gleason score $>3 + 3$) than a negative MRI (43% vs 27%) [42]. Therefore, mp-MRI is currently encouraged in men after an initial diagnosis of low-risk PCa at ultrasound-guided biopsy to rule out the presence of misdiagnosed higher-grade disease at initial biopsy.

4.2. mp-MRI before confirmatory biopsy

4.2.1. Statement

mp-MRI should be performed before a confirmatory biopsy done within 12 mo after initial diagnosis. At confirmatory biopsy, include systematic and targeted biopsies.

4.2.2. Scientific background

At confirmatory biopsy in men who did not receive a previous mp-MRI, the rate of PCa reclassification by using targeted biopsies ranges from 2% to 22% [33,43–46]. The added value of mp-MRI for surveillance/repeat biopsies (hence, more than 1 yr following the confirmatory biopsy assessment) has not been evaluated yet. However, combined data of confirmatory and surveillance repeat biopsies showed a PCa reclassification rate due to targeted biopsies of 2–14% [19,47,48]. The concordance of systematic and targeted biopsies at confirmatory biopsies is approximately 80%. Nevertheless, omitting systematic biopsies may induce a misclassification rate of 3–13% [33,43–45]. Therefore, systematic biopsy should always be performed, even in the presence of a normal mp-MRI. Targeted biopsies of suspicious lesions on mp-MRI are mainly performed for Prostate Image Reporting and Data System (PIRADS) ≥ 3 lesions. Although increased rates of reclassification occur in PIRADS 4 and 5 lesions, a substantial proportion of PIRADS 3 lesions show reclassification following targeted biopsies [43,44], thereby confirming the significance to biopsy PIRADS ≥ 3 lesions during AS.

4.3. mp-MRI during AS

4.3.1. Statement

At present, there are no robust published data to support the use of, or timing of, mp-MRI instead of repeat standard biopsy to detect progression over time. Therefore, at present mp-MRI should not solely replace repeat biopsy during AS. Moreover, use of mp-MRI prior to any follow-up biopsy is not supported by any strong evidence. However, it might be of interest to better target mp-MRI-detected lesions. In case of negative mp-MRI during follow-up, men should undergo systematic biopsies. In case of low-risk PCa detected at targeted and/or systematic biopsy despite a positive mp-MRI, patients should continue AS provided fulfillment of all previously listed inclusion criteria.

4.3.2. Scientific background

Although mp-MRI may be considered important in monitoring men on AS, robust data on the use of repeat mp-MRI instead of repeat biopsy in AS is currently lacking. Data supportive of a possible shift from repeat biopsy to repeat mp-MRI only are coming from single Institution series with high expertise on imaging [49,50]. Therefore, these results should be interpreted within the setting of an experimental approach without strong, prospective, multi-institutional validation. Prospective studies with clear definitions of radiological significance and progression are needed before this approach can be adopted. Indeed, it has also been shown that mp-MRI may miss up to 15% of clinically significant cancer during follow-up of AS [51]. Therefore, at present, mp-MRI cannot replace systematic, repeat biopsy in the follow-up of AS. The real pre-requisites for repeat use of mp-MRI during AS is proper quality image acquisition and expert readership. Scans deemed of insufficient quality should be repeated before biopsy as done in a recently published, prospective protocol [39].

5. Optimal follow-up schedule

5.1. Statement

The follow-up strategy still relies mainly on clinical and biopsy assessment. It is based on serial digital rectal examination (at least once a year), PSA (at least once every 6 mo), and repeated biopsy (at a minimum interval of 3–5 yr). mp-MRI cannot be used as a stand-alone tool to trigger follow-up biopsies.

5.2. Scientific background

Follow-up schedules of the largest AS series are reported in Table 2. Based on two single-center studies [50,52], not all patients with progression/reclassification at biopsy had radiological progression and vice versa. Therefore, mp-MRI cannot be used as a stand-alone tool to trigger follow-up biopsies; however, efforts are being made to define and standardize radiological progression during AS [53]. Moreover, radiological progression alone is not a trigger “per se” for any active intervention. However, at follow-up biopsy,

mp-MRI can be useful to decrease the number of cancers reclassified as high grade and thus suitable for active treatment. Nevertheless, whether this leads to better cancer control rates over time is yet to be determined. Results from ongoing randomized trials, The Study of Active Monitoring in Sweden [54], and the SPCG17: Prostate Cancer Active Surveillance Trigger Trial (NCT02914873), will show relevant data regarding the optimal follow-up schedule.

6. Expanding indications for AS: The EAU perspective

6.1. Inclusion of “low-volume” Gleason score 3+4

6.1.1. Statement

Despite the evidence that some men with Gleason 3 + 4 may have favorable final pathology and good outcomes on AS, it is clear that these men have an increased risk of clinical progression and the development of metastasis when monitored using an AS protocol. If men with limited Gleason 3 + 4 at biopsy decide to undergo AS, this should be done within a standardized protocol where patients are correctly informed about the lack of robust data and the increased risk of progression.

6.1.2. Scientific background

Although most published data on AS has focused on men with very low- and low-risk PCa, patients and practitioners continue to question selection criteria for this approach. Some have advocated expanding these to include men with intermediate-risk features. Three groups, Sunnybrook (Toronto, Canada), Royal Marsden (London, UK), and UCSF (San Francisco, CA, USA) included intermediate-risk patients in prospectively collected AS cohorts.

In the Sunnybrook surveillance cohort, 22% were intermediate risk, with Gleason <3 + 4 and/or PSA 10–20 ng/ml. One third of these men were aged < 70 yr. The analysis of this group has provided some important observations. Despite close monitoring and intervention for evidence of risk progression, the 15-yr PCa metastasis-free survival was 84% (3.7 times higher in the intermediate- than in low-risk group) [55]. This increase in risk was associated almost solely with the presence of Gleason 7 cancer at initial diagnosis. The hazards ratio for 15-yr PCa mortality for Gleason 3 + 4 compared to 3 + 3 was 4.0; for Gleason 4 + 3, it was 10.5. Amongst this group, the actuarial 15-yr metastasis rate was at least 20% [8]. Importantly, a PSA above 10 did not confer a significant increased risk of metastasis in the absence of Gleason pattern 4 PCa.

The Royal Marsden group also took an inclusive approach to eligibility. In their cohort, 7% had Gleason 7 disease. The presence of Gleason 7 disease was associated with a 3.4 greater likelihood of finding “adverse pathology” on subsequent biopsy [56]. Of the two PCa deaths in their cohort, one was in a patient with Gleason 7 at baseline. A limitation of many reports of conservative management of intermediate-risk disease is the relatively short duration of follow-up.

UCSF [57] reported no difference in biopsy progression or treatment rates between low and intermediate CAPRA score

patients, albeit with 47 mo of follow-up. It is plausible from these low mortality rate differences that some patients with intermediate-risk features are surveillance candidates. In particular, these are patients with low volume of disease and older age [31,58]. Another yet retrospective assessment of AS for intermediate-risk PCa is derived from the National Prostate Cancer Register of Sweden [59] that compared outcomes of 4163 intermediate-risk patients who were managed with AS (23%), radical prostatectomy (52%), and radiation therapy (25%). Amongst patients with intermediate-risk disease, the PCa mortality was 5.2% in the AS group, 3.4% in the radical prostatectomy group, and 3.8% in the radiation therapy group. These figures are similar to those reported in the Sunnybrook cohort.

Finally, a study from four centers of the European Randomized Study of Screening for Prostate Cancer included 50 men affected by Gleason score 7 and initially managed expectantly. Despite median follow-up was 2.6 yr, the 6-yr CSS (nine patients at risk) was 100% and sharply contrasted with the 68% OS [60].

7. Patient age and AS: Are there any lower or upper age cut-off?

7.1. Young patients

7.1.1. Statement

After appropriate risk stratification, patients should be counseled that outcomes of AS appear similar between younger and older patients, albeit that younger men need longer follow-up. Therefore, young age is not a preclusion from AS. However, young patient (<55 yr) with long life expectancy (ie, >20 yr) need to be counseled regarding the lack of robust data at very long-term follow-up, although they may also have more to gain from delaying radical therapy for many years.

7.1.2. Scientific background

Overtreatment of low-risk PCa is a major concern because of the associated side effects heavily influencing quality of life, particularly in younger men. However, inclusion of younger patients in AS programs is still a matter of controversy given their very long life expectancy and the ultimate need for definitive therapy. Despite this concern, it has been reported that outcome of younger men on AS are even better than their older counterpart, mainly due to lower rates of upgrading. A recent study focused on a large cohort of patients ($n = 1433$) provided evidence regarding the validity of AS for young patients [61]. Younger age was independently associated with a lower risk of Gleason score upgrading. The biopsy-based Gleason score upgrade-free rate was 73% at 3 yr and 55% at 5 yr for men aged ≤ 60 yr, compared to 64% and 48%, respectively, for men aged ≥ 60 yr ($p < 0.01$). Consequently, younger remained longer on AS. In addition, there was no association between younger age and risk of definitive treatment or biochemical recurrence after delayed radical prostatectomy. The study showed that after appropriate risk stratification, patients may be counseled that outcomes are similar among younger and older

patients at intermediate follow-up. Therefore, younger patients should be advised that intermediate-term outcomes are not worse, but that very long-term follow-up is still needed. Moreover, younger patients should also be counseled about the need for longer periods of adherence to standardized AS protocols as well as about a possible impact of multiple biopsies on functional outcomes at least after radical prostatectomy although this is still a matter of debate [62,63].

7.2. Elderly patients

7.2.1. Statement

Individual health status and comorbidity, rather than age itself, should be used to decide treatment for an individual's PCa. A life expectancy of 10 yr is most commonly used as threshold for deciding on AS rather than on watchful waiting, although this can be questioned as all the available data suggest the risk of harm in <15 yr for these patients is minimal.

7.2.2. Scientific background

Evaluation of health status and life expectancy is fundamental in clinical decision-making on treatment of PCa. In localized disease, >10 yr of life expectancy is considered mandatory for any benefit from local treatment [15]. The International Society of Geriatric Oncology PCa working group recommends that treatment for senior adults should be based on a systematic evaluation of health status using the Geriatric 8 (G8) screening tool [64]. Healthy patients with a G8 score >14 or frail patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Disabled patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment. Patients with a G8 score ≤ 14 should undergo a full geriatric evaluation as this score is associated with 3-yr mortality, assessing comorbidity, nutritional status, and cognitive and physical functions to determine if the impairment is reversible [65].

8. Race and AS

8.1. Statement

Given the lack of prospective data on AS outcomes stratified according to race, patient race should not modify eligibility to and follow-up during AS.

8.2. Scientific background

Previous studies have reported higher rate of occult co-existent cancer in low-risk African-American patients as well as higher rates of biochemical recurrence after surgery [66,67]. However, one large recent study of the SEARCH database including 40% African-American men with low-risk cancer showed no difference in pathological upstaging or biochemical recurrence, reinforcing the use of surveillance in these men [68]. No strong data exist suggesting different

biological profile of different patient races in men suitable for AS. Moreover, no strong data support any indication for genetic mutation assessment in men either candidate or on AS, regardless of patient race. African-American men should be informed that they are more likely to harbor anterior and potentially higher-grade tumors that may have implications for enrolment into AS programs [69,70].

9. Use of biomarkers in AS

9.1. Statement

Biological markers, including PSA isoforms, urine PCA3, TMPRSS2-ERG, 4K score, or GPS appear promising to guide care of men with AS. However, they have not yet been prospectively robustly tested in the AS setting. Therefore, while waiting for further data and even though some men may benefit for assessment of these biomarkers, their use cannot be currently routinely recommended in AS.

9.2. Scientific background

9.2.1. [-2]proPSA and Prostate Health Index

[-2]proPSA and Prostate Health Index, measured at diagnosis or during AS, have discriminatory power for the endpoint unfavorable histopathological reclassification according to the Epstein criteria [71–73]. Data are missing on its additional value compared with classical parameters. In terms of clinical utility, the discriminatory power is similar among studies [74].

9.2.2. PCA3 and TMPRSS2:ERG score

PCA3 and TMPRSS2:ERG seem to stratify the risk of having aggressive cancer as defined by tumor volume or Gleason score. However, they did not show any added or discriminatory and independent value compared with PSA for prediction of Gleason score ≥ 7 tumors [75].

9.2.3. 4Kscore

The 4Kpanel has been significantly associated with reclassification at the first surveillance biopsy, providing incremental value over routine clinical information, and the 4K model performed significantly better than the base model. However, the 4Kpanel did not add predictive value to a PSA clinical model for biopsy decision-making for men at subsequent surveillance biopsies [76].

9.2.4. Genomic markers

Three genetic tissue assays (Genomic classifier, Genomic prostate score, and Cell cycle progression) have been approved by the FDA for men with PCa. Genomic classifier is a score calculated from a gene-expression microarray analysis of 22 genes on formalin-fixed paraffin-embedded prostate tumor tissue, ranges between 0 and 1, and classifies patients into three risk categories [77]. Genomic prostate score is a biopsy-based 17-gene score that improves prediction of the presence or absence of adverse pathology and may help men with PCa make more informed decisions between AS and immediate treatment [78]. Cell cycle

progression test is a genomic test designed to help provide an individualized assessment of the risk of disease progression in patients with low- and intermediate-risk PCa [79]. While these genomic markers may be used to optimize patient classification and management, none of these tests has yet been specifically validated as providing substantial benefit in the AS population. However, the “sweet spot” for molecular biomarkers is the otherwise favorable-risk patient with small amount of pattern 4 (Grade Group 2) on biopsy who prefers a conservative approach if possible. A low score on a validated molecular assay provides a reassurance about the safety of nonintervention.

The inclusion of biomarkers into multivariable models may help improving the ability to predict patient outcomes on AS. A recent study evaluating nomograms based on clinical variables alone found indeed modest ability of these models to predict cancer and clinical progression during AS [80].

10. Patient distress during AS: The role of psycho-oncologist

10.1. Statement

Patient distress should not necessarily trigger radical treatment. Men with favorable-risk PCa suitable for AS should be properly reassured about the safety of this approach. Therefore, psycho-oncological support in men on AS is encouraged to minimize patient distress and optimize adherence to AS.

10.2. Scientific background

Patient preference accounts for approximately 6% of reasons for discontinuing surveillance [7]. Moreover, patient preference is related to non-adherence, which in the end may lead to discontinuation. To reduce distress frequently experienced by men diagnosed with PCa and their partners, the following steps are needed: (1) improved community and medical awareness of AS, (2) consistent information about the safety of AS which does not decrease the rates of curability of active treatment when delivered, (3) appropriate counseling on when radical treatment is required, and (4) consistent, unbiased information on treatment options, prognostic indicators, and side effects. Finally, regularly updated decisional support information/aids incorporating men's values are necessary [81,82].

11. When to end AS

11.1. Statement

The decision to deliver active treatment should be based on the deterioration (ie, disease progression) of the prior inclusion criteria (Table 1). A worsening in mp-MRI features such as increased volume of the index lesion, appearance of new lesions or increased PIRADS score at a given lesion do not represent “per se” trigger for intervention. Rather, these parameters should be used to optimize timing, targeting, and extent of biopsies. When the life expectancy decreases,

the decision to remain on AS despite increasing in PCa grade should be individualized. However, in case of a decrease in life expectancy to <10 yr, a switch from AS to a watchful waiting protocol is indicated.

11.2. Scientific background

Need for active treatment is based on a change in grade, or in the extent of cancer involvement at biopsy or in local stage (>T2). These criteria are well recognized in all published cohorts [83]. A PSA change (especially a PSA doubling time of <3 yr) is a less powerful indicator to change management based on its weak link with grade progression [84,85]. Similarly, it seems to be a less power predictor of disease reclassification and progression [10]. Active treatment may also be delivered upon patient request. This occurs in around 10% of patients on AS [7]. While mp-MRI may show worsening of PIRADS score or appearance of new lesions or increasing in volume of the index lesion, these parameters should not be used per se to trigger intervention. Imaging features should instead be always complemented with targeted and systematic biopsies, which may confirm local disease progression. Even at follow-up biopsies, targeted biopsy should be always performed with systematic sampling, given the association between PIRADS score of the IL and the risk of missing significant PCa outside the IL [51,86]. Finally, since 25–40% of men remain on AS at 10 yr of follow-up [7,30], the decision to continue on AS in these men with decreasing life expectancy despite increasing in PCa grade should be individualized. In men with a decreased life expectancy to <10 yr based on careful patient assessment including change in comorbidity profile over time, a switch from AS to watchful and waiting is indicated.

12. Conclusions

AS should be considered for all men with low-risk PCa, fit for curative treatment, and willing to adhere to AS protocols, including younger men who are provided accurate assessment to exclude misclassification of higher-grade disease. However, men with very long life expectancy should be counseled about the lack of very long-term data of AS. Consider central pathological review of the biopsy specimens in patients within AS programs, especially when recommendations for reporting criteria are not respected. While use of biomarkers cannot be routinely recommended in AS, mp-MRI can be used to optimize the diagnosis of clinically significant PCa in order to improve patient selection and reduce the rates of misclassification. The strongest evidence available is in favor of the use of mp-MRI prior to confirmatory biopsy. Although the role of imaging is increasing even during AS, the follow-up strategy still relies mainly on clinical and biopsy assessment. It is based on serial digital rectal examination (at least once/year), PSA (at least once every 6 mo), and repeated biopsy (at a minimum interval of 3–5 yr). Currently, mp-MRI should not be used as a stand-alone tool to trigger follow-up biopsies or active intervention. The decision to deliver active treatment should

be based on the deterioration (ie, disease progression) of the prior inclusion criteria used at AS initiation. Finally, the position of the EAU will be updated after a formal consensus meeting and a formal systematic review on AS which will be available in early 2019. While waiting for such consensus, the current statements represent the formal position of the EAU on AS and they complement the EAU guidelines.

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Acquisition of data: Briganti, Fossati, Catto, Cornford, Montorsi, Mottet, Wirth, Poppel.

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