Active surveillance in prostate cancer management: where do we stand now?

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Abstract

Prostate cancer (PCa) is the most common cancer in men, with a steadily rising incidence, affecting on average one in six men during their lifetime. The increase in morbidity is related to the increasing overall life expectancy, prostate-specific antigen testing, implementation of new molecular markers for cancer detection and the more frequent application of multiparametric magnetic resonance imaging. There is growing evidence demonstrating that active surveillance (AS) is an alternative to immediate intervention in patients with very low- and low-risk prostate cancer. Ongoing reports from multiple studies have consistently demonstrated a very low rate of metastases and prostate cancer specific mortality in selected cohorts of patients. As a matter of fact, AS has been adopted by many institutions as a safe and effective management strategy. The aim of our review is to summarize the contemporary data on AS in patients affected with PCa with the intention to present the most clinically useful and pertinent AS protocols.

Key words: active surveillance, prostate cancer, molecular markers, multiparametric magnetic resonance imaging.

Introduction

Prostate cancer (PCa) is the most frequently diagnosed non-skin cancer among European men [1]. This malignancy affects mainly senior men aged 60 and above. Factors known to be associated with the development and progression of PCa are age, family history, and ethnicity, with age being the most important one. Golabek *et al.* [2] also found that excess calcium intake (dietary supplements and food) may increase the risk level of PCa. Most of the diagnosed tumors are of indolent nature and, importantly, only a small number of prostatic malignancies have aggressive clinical behavior that requires immediate treatment.

In addition to the group of diagnosed patients, there is a large number of undiagnosed patients who do not experience any side effects of their illness. This is revealed in the results of post mortem examinations. In the group of men aged over 60 years, PCa was observed in more than 40% of cases. In the group of men over 80 years nearly 60% were harboring the disease [1, 3].

The standard treatment of PCa in intermediate- and high-risk groups remains radical prostatectomy or radiotherapy. Radical treatment is re-

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lated to complications, which frequently significantly affects the patients' quality of life.

Active surveillance (AS) is a new strategy for the management of patients with low-risk PCa, aiming at postponing treatment until the cancer becomes clinically significant. The intention is both to increase patient quality of life by avoiding the consequences of treatment-related side effects and to lower socio-economic costs. This approach is based on the fact that most PCa patients are asymptomatic for life and treatments involve risks of major complications including erectile dysfunction and incontinence. Treatment of PCa is only implemented when the disease progresses.

Many diagnostic tests are used to assess the stage of disease, such as prostate biopsies, serum markers (PSA), magnetic resonance imaging (MRI) and genetic markers that are just being implemented and whose usefulness is only now being studied [4–7].

This review aims to gather knowledge about AS and to assess its practical clinical use along with the assessment of new indicators that could improve AS protocols [8].

Evidence acquisition

The authors of this review have systematically reviewed the PubMed database. From this database the 44 most recent articles on AS of PCa were selected, including incorporation of the latest National Comprehensive Cancer Network (NCCN) and European Urology (EAU) guidelines. Selection of articles was performed according to preferred reporting items for systematic reviews and meta-analysis statement guidelines. The review was about a comprehensive analysis of AS including methods that could help in its improvement. The authors searched for articles using the key words active surveillance, prostate cancer, molecular markers, mpMRI. The authors focused on selecting the latest publications (last 2 years). Among the previously published articles, those with a large number of citations were selected (min. 70).

Active surveillance idea

Active surveillance is a management strategy that aims to avoid invasive therapy among patients with clinically insignificant tumors [4, 7]. Instead of immediate treatment, regular diagnostics and follow-up investigations are started to assess the progression of the disease. The advantage of AS is to delay the side effects of treatment or to avoid them completely if the cancer does not become clinically significant. In addition, the patient, when postponing the treatment, can rely on the fact that when therapy is implemented in the future, new, potentially more effective, therapeutic options will be available [6].

It is of utmost importance to distinguish between AS and watchful waiting (WW). Both strategies involve postponing treatment, but there are significant differences between them. Active monitoring is intended for younger men – with a long, over 10 years life expectancy. In contrast, watchful waiting is for elderly men – with an estimated survival below 10 years. In addition, WW, unlike active monitoring, focuses on managing diseases that pose a direct threat to life and/or quality of life. Patients who decide to be vigilant may from time to time perform a PSA blood test, but there is no need to repeat the prostate biopsy. In the case of AS, the main focus is on the control of cancer progression and in this case invasive tests are not abandoned [8–10].

Limitations of active surveillance

The potential AS drawbacks involve: (1) a potential delay of the treatment of aggressive cancer (2) and psychological strain.

1) AS is characterized by a statistically higher incidence of disease progression and metastases than radical surgery or radiotherapy. However, according to the study results, at a median 10 years follow-up, active monitoring does not lead to an increase in PCa specific mortality [11, 12].

2) An inseparable aspect that should accompany AS should be care for the patient's psychological comfort. From the moment of diagnosis, the patient's life is often subordinated to medical procedures and the endless diagnostic process. In addition, the patient must struggle with uncertainty about his own future – never knowing when the disease will escalate. Patients with fear may refuse AS because they do not allow themselves to think about not treating the disease. The additional stress related to AS might decrease the comfort of life [13–15].

Active surveillance protocols

There are many protocols devoted to AS in the management of PCa. Only asymptomatic patients with clinically insignificant, low-volume neoplasms – characterized by slow growth kinetics – can be included in the AS protocol. The PCa division system uses the following criteria [7]:
– PSA blood concentration,
– prostate biopsy result based on the Gleason scoring system,
– T, N, M classification.

The risk group is determined based on the values of different parameters. Knowing the stage helps to decide what type of treatment would be the most appropriate for the patient and can help to predict the disease prognosis. Depending on the protocol (Table I [10, 11, 16–23]), different

Table I. Available protocols for active surveillance programs

Study	Monitoring protocols for active surveillance				Criteria for active surveillance		
	Confirmatory biopsy, from diagnostic biopsy [years]	Repeat biopsy [years]	PSA testing [month]	Rectal examination [month]	Clinical stage	PSA [ng/ml]	Gleason score
NCCN guidelines [10]	Undefined	Not more often than 1	Not more often than 6	Not more often than 12	≤ T2A	< 10	≤ 6 or Gleason grade group 1
EAU guidelines [11]	Undefined	Undefined	Undefined	Undefined	cT1–2a	< 10	< 7
Bokhorst et al. [16] (PRIAS, multinational)	1	3 for the first 10 years	3–6	–	≤ T2	≤ 10	≤ 6
Welty et al. (UCSF, San Francisco, CA) [17]	1	1–2	3	6	≤ T2	≤ 10	≤ 6
Selvadurai et al. (Royal Marsden Hospital, London, UK) [18]	1.5–2	2	3–6	3–6	≤ T2	< 15	≤ 6 or 3 + 4 = 7
Thompson et al. (St. Vincent's Prostate Cancer Centre, Sydney, Australia) [19]	1	1–2	3–6	6–12	≤ T2a	< 10	≤ 6
Thomsen et al. (University of Copenhagen) [20]	1	Variable	3	3	≤ T2a	≤ 10	≤ 6
Soloway et al. (University of Miami, Miami, FL) [21]	< 1	1	3–6	3–6	≤ T2	≤ 10	≤ 6
Klotz et al. (Sunnybrook Health Sciences Centre, Toronto, Canada) [22]	1	3–4	3–6	–	–	≤ 10	≤ 6
Tosoian et al. (Johns Hopkins University, Baltimore, MD) [23]	1	1–2	6	6	T1c	–	≤ 6

groups are distinguished, i.e. five risk groups according to the NCCN [10] and three as per EAU guidelines [11]. Despite the existence of various protocols, the classification groups for AS are characterized by the following criteria: PSA < 10 ng/ml, GS < 7 and cT1-2a. The above-mentioned methods are used not only to include patients in the AS, but they are also used to assess the extent of the disease. The biopsy result is considered the most relevant, but it is far from ideal. Prostate biopsy is an invasive procedure, which might lead to complications, and it is not 100% accurate. That is why additional tools are being developed to improve the AS inclusion criteria and AS follow-up protocols. Monitoring in the AS consist of regular outpatient appointments, which usually involve digital rectal examination (DRE), PSA testing and biopsy. The frequency of these tests varies depending on the protocol.

Diagnostic tools

Every patient eligible for AS requires a precise diagnostic process and regular testing. The main aim of these actions is to assess the disease progression. Fundamental techniques used in diagnosing and monitoring patients with PCa are PSA, biopsy and multiparametric magnetic resonance imaging (mpMRI). Additionally, to increase the effectiveness of AS, there is a possibility to use genetic testing: PCA3 score, PHI score, 4K score, SelectMDx, ConfirmMDx and TMPRSS2-ERG gene fusion. Although the new genetic markers are not used in the current AS protocols, they appear very

helpful in identifying men with potentially aggressive disease among patients with low PSA levels. Importantly, in the above group, biomarkers are able to correct for too low accuracy of PSA alone.

Multiparametric magnetic resonance imaging

The use of multiparametric MRI (mpMRI) allows early detection of clinically significant PCa. It combines T2-weighted imaging (T2WI), dynamic contrast-enhanced imaging (DCEI) and diffusion-weighted imaging (DWI), but T1-weighted imaging (T1WI) is additionally used to show any hemorrhage or other changes. The radiologist grades the lesion by the PI-RADS five-point scale. The lower the value, the less aggressive the lesion is:
– PI-RADS 1: very low (presence of clinically significant tumor is low probable),
– PI-RADS 2: low (presence of clinically significant tumor is low probable),
– PI-RADS 3: intermediate (presence of clinically significant tumor is ambiguous),
– PI-RADS 4: high (presence of clinically significant tumor is probable),
– PI-RADS 5: very high (presence of clinically significant tumor is probable) [24, 25].

These days, the second version of this algorithm has been developed and new studies about its utility are being performed. Hoffmann *et al.* [25] compared PI-RADSv1 and PI-RADSv2 and they did not find any difference in accuracy to predict clinically significant PCa. They also found that mpMRI accuracy in detecting anterior tumors was about 86–88%. On the other hand, Kasel-Seibert *et al.* [26] found that when it comes to suspicious intraprostatic lesions, PI-RADSv2 could be a reliable tool, especially when its value is ≥ 3. The Kasel-Seibert *et al.* study included experienced and inexperienced readers. The main aim of creating PI-RADSv2 was to improve diagnostic quality, and the study [27] confirmed that PI-RADSv2 was more accurate than PI-RADSv1. According to PI-RADSv2, a score ≥ 3 appears to be much more specific, when considering if the patient should undergo repeated biopsy, than PSA level. The algorithm can also fail when it comes to anterior lesions – a malignant lesion can be described as benign by the radiologist following the algorithm, but the targeted biopsy appears positive, showing aggressive lesion. It can occur as a result of insufficient practice by the radiologists, as it is a relatively new method. According to many studies, PI-RADSv2 has a very high negative predictive value (NPV) and by itself remains an essential diagnostic tool. MpMRI may successfully confirm low-risk PCa, allowing repeat prostate biopsy to be avoided. The sensitivity of mpMRI in PCa diagnosis was 72.9–97.6% [28], the specificity 81.25% [29].

Prostate biopsy

Biopsy remains essential in PCa diagnosis. There are a several kinds of biopsy – standard, saturation and fusion biopsy. Referral to standard biopsy is based on elevated PSA levels and/or suspicious digital rectal examination (DRE). In a standard biopsy protocol, 12 samples are taken. Saturation biopsy is much more extended – it includes 20 or more samples and is performed under general anesthesia. Fusion biopsy is a relatively novel approach, which combines mpMRI and transrectal ultrasound (TRUS) images. A radiologist analyzes the mpMRI image and marks the boundaries of the lesion. While performing a biopsy, TRUS-MRI fusion imaging is used to take samples of the lesion, which was observed on MRI. Interestingly, Pepe *et al.* [30] compared saturation and fusion biopsy, as tools for monitoring patients during AS. The study revealed higher diagnostic accuracy of saturation biopsy than that of the fusion procedure. Although the detection rate was really high for saturation biopsy, which shows its utility, the lower detection rate for fusion biopsy might be due to the low quantity of samples (on average, 4 cores). Another study of Pepe *et al.* [31] included 75 men eligible for AS, who underwent mpMRI before confirmatory extended biopsy. Confirmatory biopsy is a follow-up test, to provide the most accurate diagnosis to the patient, and make sure there is no occurrence of underdiagnosing or underclassifying the lesion. The results showed that 28% of men were reclassified by saturation biopsy (30 cores) combined with fusion biopsy (4 cores), which proved Gleason score ≥ 7. The authors stressed the importance of the combination of mpMRI and confirmatory biopsy, to obtain the most reliable diagnostic result.

Markers

Prostate-specific antigen

Prostate-specific antigen concentration although still frequently used remains a controversial clinical test to assess the risk of diagnosis of PCa. First of all, PSA lacks specificity. Secondly, it frequently leads to overdiagnosis and overtreatment of clinically insignificant disease. The current approach suggests that increased PSA levels should be combined with other diagnostic tools. Bancroft *et al.* [32] performed a study where men aged 40–69 years had PSA testing, and those with a PSA level > 3 ng/ml were offered a prostate biopsy. 162 men underwent a biopsy, 59 cancers (intermediate or high-risk) were detected and 42 of them were carriers of BRCA1 or BRCA2 gene mutation. That suggests a correlation between elevated PSA levels and a possible aggressive lesion in the prostate in BRCA1/2 mutation carriers.

The PSA test is not confined to total PSA plasma concentration – also pro-PSA level, PSA density and free PSA can be measured [10]. When it comes

Table II. Diagnostic accuracy of PCa molecular markers

Diagnostic tool	Sensitivity (%)	Specificity (%)	Author
PCA3	47–66	60–76	Nickens *et al.* [37]
PHI score	90–97.90	31.1–38.00	Kretschmer *et al.* [38], Tosoian *et al.* [39], Loeb S *et al.* [40]
SelectMDx:			Van Neste *et al.* [41]
HOXC6	90	33	
DLX1	83	16	
HOXC6 + DLX1	91	36	
ConfirmMDx	68.00	64.00	Stewart *et al.* [42]

to aggressive tumors, elevation of pro-PSA levels seems to be a more accurate diagnostic tool [33]. PSA density is the quotient of total PSA level divided by prostate gland volume, and the higher it is, the higher is the likelihood of detecting a clinically significant disease [33].

Prostate cancer antigen 3

Prostate cancer antigen 3 (PCA3) is a non-invasive diagnostic tool describing expression of PCA3 RNA. During DRE the prostate massage is performed and the urine sample is taken after. This test is based on RNA PCA3/RNA ratio × 1000. An elevated (higher than 35) PCA3 score correlates with a higher risk of positive prostate biopsy [34, 35]. PCA3 provides higher diagnostic accuracy than serum PSA concentration. Although the PCA3 test appears helpful in identifying men with potentially aggressive disease requiring immediate treatment, the prognostic value of the test has been questioned [36] (Table II [37–42]).

Prostate health index score

The prostate health index (PHI) score is a combination of three PSA isoforms: total PSA, ratio of total and free PSA (%fPSA) and proPSA. It was created to improve the specificity of PSA testing [39]. However, PHI density, compared to the PHI score alone, is even more precise, showing 97.9% sensitivity and 38% specificity for clinically significant PCa [38, 39].

4Kscore

The 4Kscore includes total plasma PSA, free PSA, intact PSA (inactive PSA form) and human kallikrein-2 (hk2). Kallikrein-2 is a protease whose expression was found in the prostate gland. Combining the 4Kscore with patient's age, DRE and biopsy results forms the 4Kscore Test. This test is mainly used for assessing the risk level for diagnosing PCa [9, 38].

SelectMDx

The test measures the mRNA levels of the (urinary homeobox C6-HOXC6 and distal-less

homeobox 1-DLX1) biomarkers, using kallikrein KLK3 expression as an internal reference, to aid in patient selection for prostate biopsy. Higher expression levels of DLX1 and HOXC6 mRNA are associated with an increased probability for high-grade Gleason score PCa. The assay is performed on post-DRE urine samples. Several recent studies revealed that using SelectMDx might reduce the overdiagnosis of clinically insignificant disease and by such means might lower the overtreatment of PCa [38].

ConfirmMDx

ConfirmMDx is an assay which checks the epigenetic alterations (precisely the methylation status) of many oncogenes (incl. Ras) from the patient's last negative biopsy. The basis of using ConfirmMDx is to discover the "halo effect" that tumor cells effuse by their epigenome, because it can be the very first symptom of a growing lesion that can be seen by the pathologist. ConfirmMDx may also be a predictor of a further negative biopsy [9, 38].

TMPRSS2-ERG

TMPRSS2-ERG is a fusion of TMPRSS2 and ERG genes, which can be detected in more than 50% of PCa patients. TMPRSS2 is a gene which encodes a serine protease. The exact function of this gene's protein is still unknown, but it is regulated by androgens. ERG is a transcription factor from the family of ETS factors, which controls cell differentiation and apoptosis. TMPRSS2-ERG gene fusion occurrence combined with elevated PCA3 improves both sensitivity and specificity of these tests in PCa detection [43]. Furthermore, TMPRSS2-ERG fusion may be associated with resistance to androgen deprivation therapy [44].

Cost-effectiveness

To assess the cost-effectiveness of AS, many factors have to be taken into account. In the case of patients without progression of the disease, no costs associated with the therapy will arise at all. Howev-

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er, one should take into account the costs resulting from the necessity to carry out regular diagnostic tests. It should be mentioned, however, that such tests would also be performed in people after the therapy as recurrence control instead of prognosis control. The potential additional cost of AS seems to be limited only to a group of patients who are not properly diagnosed and whose treatment costs will probably be higher due to the late start of treatment. The health aspect should also be taken into account when continuing the AS assessment. Due to postponing the treatment, the life of patients will not worsen as a result of its side effects. As a consequence, they will maintain full efficiency of work and will not require financial outlays in the form of allowances and maintenance bonuses.

Conclusions

Active surveillance seems to be an appropriate solution for selected patients harboring a low risk PCa. Compared to radical treatment AS: (1) helps to avoid unnecessary treatment and (2) enables maintaining the quality of life together with normal activities. In addition, (3) AS allows the costs of treatment to be reduced. The potential drawbacks of AS which should be considered include: (1) psychological strain and (2) a potential delay of the treatment of aggressive cancer. There is also (3) a need for regular follow-up investigations including frequent imaging studies and biopsies. The authors of the review recommend the use of AS for every patient diagnosed with low-risk prostate cancer meeting the inclusion criteria for the AS protocol. The stringent follow-up of PCa patients under AS is necessary to implement the necessary treatment as soon as there is disease progression or the cancer becomes aggressive.

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Conflict of interest

The authors declare no conflict of interest.

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