Review

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Contemporary Role of Active Surveillance in Prostate Cancer: To Whom, When, How?

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Abstract

Due to the widespread use of prostate-specific antigen testing and the increase in the elderly population, many asymptomatic patients have started to be diagnosed with prostate cancer (PCa). This leads to the reality of overdiagnosis and overtreatment of PCa. Since most of the initial diagnoses are clinically insignificant, a concept called active surveillance (AS) has emerged in the treatment of PCa, especially for patients in the low-risk group. Some authors also recommend this approach to selected intermediate-risk group patients. The main goal of AS is to prevent the negative effects of radiotherapy and surgery. Several well-known clinicians reported their results on AS, and their criteria appear to differ in terms of patient selection and follow-up. We aimed to review the criteria for patient selection, follow-up principles, and the outcomes of AS.
Keywords: Prostate cancer, active surveillance, treatment

Introduction

Prostate cancer (PCa) is the most common cancer among men and the second most common cause of cancer-related death among men (1). The probability of developing invasive PCa from birth to death is 1 in 8 (1). With the widespread use of prostate-specific antigen (PSA), advances in prostate biopsy (PB) techniques, and the increase in the elderly population, many asymptomatic patients have started to be diagnosed with PCa. Although this situation reduces deaths due to PCa, it causes overdiagnosis and overtreatment issues (2). PCa is a predominantly biologically slow-progressing pathology and does not affect survival or cause lifelong symptoms in a group of patients. Additionally, many incidental PCa are detected in autopsy studies. Estimated mean PCa prevalence was found to increase non-linearly in autopsy studies from 5% under 30 years of age to 59% over 79 years (3). For this reason, it was thought that many patients with PCa could be followed up with active surveillance (AS). In a prospective AS study of grade group (GG) 1 PCa patients, the cumulative incidence of PCa-specific mortality or metastasis was 0.1% at 10 and 15 years (4). Moreover, 10 and 15-year cancer-specific survival (CSS) were observed as 98.1% and 94.3% in patients in AS (5). Patients with AS die from reasons other than PCa, such as cardiovascular causes, and the 15-year CSS and overall survival (OS) were 99.9% and 69%, respectively (6).

Simply put, AS is meant to avoid overtreatment and to provide proper treatment to patients with localized PCa at the appropriate time with a curative intent (7). AS also aims to protect patients from treatment-related side effects. The impact of AS on cancer-specific quality of life is noticeably less than the other two treatment options. The effects of radical prostatectomy (RP) on urinary and sexual function, and radiotherapy (RT) on bowel function, are well known, whereas these are not affected in AS (8). Urinary incontinence, erection, and sexual dysfunction are more common in patients with RP (9).

All of these facts have caused the use of AS to increase over time. In the USA, the use of AS and watchful waiting (WW) in low-risk prostate cancer (LRPCa) patients increased from 14.5% to 42.1% from 2010 to 2015, while the use of local curative treatments, RP and RT, dramatically decreased (10). According to European Association of Urology (EAU) guidelines, AS aims to delay or prevent unnecessary treatment and unnecessary

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treatment-related side effects in clinically localized PCa patients with a life expectancy of more than 10 years (11). It also aims to ensure the right timing for curative treatment. So, it is important for patients receiving AS to know that PSA monitoring, clinical examination, imaging, and repeat biopsies should be performed in a pre-planned follow-up strategy. As a result of these reassessments, patients may need to receive radical curative treatment. In this review, we aimed to review guidelines and protocols used in AS and we report the criteria of patient selection, follow-up principles and the outcomes of AS.

Which Patients are Eligible for Active Surveillance in Prostate Cancer?

AS is not WW; it aims to protect patients from the side effects of treatment, but also provides the right curative treatment if necessary at the appropriate time. It is still not clear how to identify patients with clinically insignificant PCa. Studies on AS are generally observational, and there are no strict criteria for patient selection and follow-up schedules (Table 1) (5,12-14). However, certain features look similar in describing eligible patients such as LRPCa patients with a Gleason score (GS) of 3+3, a PSA level less than 10 ng/mL, and a clinical stage less than or equal to cT2a. Initially, AS should be recommended to patients with localized PCa in LRPCa (15). Some studies also included intermediate-risk prostate cancer (IRPCa) patients. However, AS in intermediate-risk patients is a controversial issue and appropriate patient selection remains unclear. This topic is discussed in detail later.

Selection of eligible patients is critical in AS. Enrolling eligible patients will protect them from the side effects of unnecessary treatment and increase the success of AS. For example, a study that selects PSA <10 ng/dL as the AS selection criteria; and a study that selects PSA <15 ng/dL will have patients with different characteristics (5,16). These small differences lead to heterogeneity of patients in the studies. Iremashvili et al. (17) compared five different AS protocols with RP pathologies in patients whose initial diagnosis was GG 1 in PB. There was Gleason 4/5 cancers in 30% of the RP specimens. Overall, 75% of patients met the criteria of at least one protocol and only 23% met the criteria for all protocols (17). One should keep in mind that the majority of LRPCa patients selected for AS treatment will not be included if we select stricter criteria. On the other hand, enrolling intermediate or higher-risk patients in AS treatment could lead to treatment failure.

In AS for selecting patients, the main idea is to have a small tumor (low number of tumor-positive cores and percentage of positive tumor), low-grade positive biopsy-proven PCa low PSA level and low PSA density in early stage [in digital rectal examination (DRE)]. The prediction of clinically insignificant PCa patients meeting this condition was defined for the sextant biopsy scheme according to the Epstein criteria (clinical stage T1c, PSA density ≤0.15 ng/mL/cm^3, GS ≤6 or stage group 1, ≤2 positive PB cores and ≤50% tumor percentage in positive PB cores) (18). However, the number of tumor-positive cores and the percentage of tumors in the cores are found to be at higher rates in 12-core PB than in sextant PB (19). 12-core PB has become the standard biopsy scheme in clinical practice over the years. Although the sextant PB scheme has a high sensitivity in detecting clinically insignificant PCa according to Epstein's criteria, 12-core PB has shown better results than sextant PB (19,20).

EAU guidelines state that the most frequently published criteria are ISUP GG 1, clinical stage cT1c or cT2a, PSA <10 ng/mL, and PSA-D <0.15 ng/mL/cc, based on systematic biopsy schemes (11). National Comprehensive Cancer Network (NCCN) defines patients with cT1c, GG 1, PSA level <10 ng/mL, <3 PB fragments/cores positive, ≤50% cancer in each fragment/core, and PSA density <0.15 ng/mL/g as very low-risk prostate cancer (vLRPCa) (21). In the 2024 guidelines, the NCCN recommends AS or observation depending on life expectancy, as the only treatment option in vLRPCa patients, owing to no difference in survival with radical treatment and to prevent the side effects of radical treatment (21). NCCN also defines patients with cT1-cT2a, GG1, and PSA <10 ng/mL as LR-PCa and recommends AS as an alternative to radical treatments (21).

How to Follow-up the Patients in Active Surveillance?

AS is a management approach for people who are diagnosed with localized PCa. It is important to provide early radical curative treatment when a higher risk or higher volume disease develops in the follow-up. Patients in AS are followed according to a scheduled follow-up protocol. Regular tests are used for monitoring, such as through PSA tests, DRE, regular biopsies, and multiparametric prostate magnetic resonance imaging (mpMRI), in recent years. The follow-up criteria of some studies are shown in Table 1. There are some differences between the follow-up protocols in the studies.

Patients may be misclassified in PB. There may be an upgrade in the pathologies of patients who are under AS according to PB pathology. In a study, 29.7% of patients with PB pathology GG 1 had higher GG in RP pathologies (22). In another study, 21.8% of patients in the LRPCa, and 13.1% of the patients in the very LRPCa experienced pathological upgrades in RP (23). Confirmation biopsy is recommended to avoid these reclassification mistakes. We define confirmation biopsy as a repeat biopsy performed within 6-12 months to exclude sampling error, especially in patients who have not undergone MRI before biopsy (11). Confirmation PB is performed soon after the first PB in AS. Compliance with the first repeat PB was estimated to be 81% in patients under AS (12). NCCN guidelines strongly recommend AS consideration within the first 6 to 12 months for patients (21).

There are differences in the timing between confirmation PB and follow-up PB in studies. Studies recommend early confirmation of PB in order to select the most appropriate patient group and not delay the treatment of unsuitable patients for AS (24). Some studies follow-up with annual PB of patients by performing a confirmatory PB in the first 3 months (24). There are also studies in which patients undergo a 2-year PB with a confirmatory PB at 6-12 months (5). In some studies, no confirmation biopsy was performed, and patients were followed up with annual prostate biopsies (25). The NCCN recommends that all patients should undergo PB within 1-2 years of their diagnostic PB (21). Analyses of four active follow-up cohort studies showed a delay of 3 to 5 months in detecting upgrading with biennial PB

Table 1. Selection criterias and follow-up strategy of active surveillance protocols

Authors reference	Article	Year	N	Age	Selection criteria						Follow-up strategy				
				Median (min-max)	Gleason score	Clinical stage	Positive core number	Single-core positivity	PSA (ng/mL)	PSA density (ng/mL)	Prostate biopsy	PSA measurement	DRE	Prostat MRI	
Tosoian et al. (25)	Active surveillance program for prostate cancer: an update of the Johns Hopkins experience	2011	769	66 (45-92)	≤6	cT1c	≤2	≤50%	<10	<0.15	Annualy	Semiannually	Semiannually	None	
Bul et al. (12)	Active surveillance for low-risk prostate cancer worldwide: the PRIAS study	2013	2494	65.8 (61-71.4)	≤6	cT1/T2	≤2	Not recorded	≤10	<0.2	1, 4, 7 years	3 months (first 2 years) / 6 months (after 2 years)	None	None	
Selvadurai et al. (16)	Medium-term outcomes of active surveillance for localised prostate cancer	2013	471	66 (51-79)	≤6 or 7 (older than 65 patients)	≤cT2a	None	≤50%	<15	Not recorded	2 years	3 months (first 2 years) / 4 months second year / 6 months (after 2 years)	3 months (first 2 years) / 4 months second year / 6 months (after 2 years)	None	
Tosoian et al. (6)	Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer	2015	1298	66 (62-69)	≤6	cT1c	≤2	≤50%	Not recorded	<0.15	Annualy	In every 6 month	Semiannually	None	
Klotz et al. (5)	Long-term follow-up of a large active surveillance cohort of patients with prostate cancer	2015	993	67.8 (41-89)	≤6 or 7 (older than 70 age patients)	≤cT2a	None	None	<10 or <15 (older than 70 age patients)	<0.15	Confirmation biopsy and 3-4 years	3 months (first 2 years) / 6 months (after 2 years)	None	None	
Godtman et al. (57)	Long-term results of active surveillance in the göteborg randomized, population-based prostate cancer screening trial	2016	244 (51%)	66 (63-68)	≤6	T1c	≤2	≤50%	<10	<0.15	Confirmation biopsy and 2-3 years	3-12 months	Semiannually	Yes, in 18 month	
			126 (27%)		≤6	T1c	Not recorded	Not recorded	<10	Not recorded					
			104 (22%)		7	T1-2	Not recorded	Not recorded	<20	Not recorded					
Tosoian et al. (4)	Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort	2020	1293	66 (61-69)	≤6	cT1c	≤2	≤%50	<10	<0.15	Confirmation biopsy and Annualy*	Semiannually	Semiannually	Yes, in 18 month	*If PIRADS 3 ≤ in prostat mr , fusion biopsy after 2014
			525	67 (62-71)	≤6	≤cT2a	None	None	≤10	None					

Table 1. Continued

Authors reference	Article	Year	N	Age	Selection criteria						Follow-up strategy				
				Median (min-max)	Gleason score	Clinical stage	Positive core number	Single-core positivity	PSA (ng/mL)	PSA density (ng/mL)	Prostate biopsy	PSA measurement	DRE	Prostat MRI	
Carlsson et al. (13)	Long-term outcomes of active surveillance for prostate cancer: the memorial sloan kettering cancer center experience	2020	2664	62 (57-68)	≤6	≤cT2b	Core Positivity = any	No restriction on number of positive biopsy cores	PSA= any	Any	Confirmation biopsy and in every 2-3 years	Semiannually	Semiannually	Yes, in 18 months	
Herden et al. (14)	Active surveillance for incidental (cT1a/b) prostate cancer: long-term outcomes of the prospective non-interventional HAROW study	2021	68	69.9 (63.6-72.5)	≤6	≤cT1a/b	≤2	Not recorded	≤10	≤0.2	First year and then after every 3 year	3 months (first 2 years) / 6 months (after 2 years)	3 months (first 2 years) / 6 months (after 2 years)	None	

PSA: Prostate specific antigen, DRE: Digital rectal examination, MRI: Magnetic resonance imaging

starting after a first confirmatory PB compared with annual biopsies (26). Despite this delay, biopsy frequencies do not seem to have a significant effect on survival among studies. Therefore, as an alternative to annual biopsies in suitable patients, biopsy frequencies may be reduced and semiannual PB follow-up may be appropriate (26).

The use of mpMRI contributes clearly to the detection of clinically significant PCa in PB. However, if biopsies were performed based solely on MRI progression findings during follow-up, approximately two-thirds of biopsies would be avoided, but 40% of patients with histological progression would be undetected (11). Therefore, protocol-based repeat PB should be performed. Studies recommend follow-up PB in AS despite differences in the timing of PB among studies. Some studies perform annual PB, while others do PB at intervals of 2-3 years (12,16,25). Although follow-up PB is recommended by AS protocols, some authors stated that repeat PB may be omitted in some patients with low PSA density (<0.15) because there is a very low risk of progression, especially in low-grade stable MRI findings (27).

PSA monitoring and DRE at an average of 3-6 month intervals are recommended by many studies in the follow-up conducted. There is no single accepted protocol for follow-up in the studies. It seems suitable for clinicians to recommend a patient-specific follow-up protocol on the basis of evidence-based medicine. The most appropriate approach is to individualize the intensity of the patient's follow-up protocol in AS according to the patient's life expectancy and re-classification risk (21).

Is Active Surveillance in Intermediate Risk Prostate Cancer Patients an Appropriate Approach?

Utility of AS in the IRPCa is controversial, and studies in this perspective are limited (16,28,29). However, in very selected patients, it might have a role (30). Unfortunately, a similar problem with the selection criteria and follow-up protocols also happens here (31). Nyame et al. (32) reported their findings in a cohort of localized PCa patients with AS. Although they prefer to restrict AS management to localized PCa patients with vLRPca and LRPca as described by NCCN criteria, they also offer AS to IRPCa and high-risk PCa patients with a life expectancy of less than 20 years. Authors report the 5- and 10-year survival rates of all intermediate and high-risk patients as 98% and 94%, respectively. Similarly, Bul et al. (33) reported a 10-year survival rate for LRPCa and IRPCa as 99.1% and 96.1% with no statistically significant difference. However, in another study, survival and metastasis-free survival rates at 5-year follow-up were similar between LRPCa and IRPCa; but worse in the IRPCa at 10-year follow-up (31). Mukherjee et al. (34) found that the 5-, 10-, and 15-year treatment-free survival rates, 5- and 10-year metastasis-free survival rates, and 5-year OS rates were similar in IRPCa and LRPCa patients, but the 5-, 10-, and 15-year CCS rates, long-term OS rates (10 and 15 years), and metastasis-free survival rate (15 years) were significantly lower in IRPCa.

It should be taken into consideration that IRPCa patients are heterogeneous. High core involvement and the presence of Gleason 4 pattern in these patients are indicators of an increased risk of progression (35). In a study of patients with LRPCa and

IRPCa, the data support the use of AS in Gleason 6 patients, but not in Gleason 7 patients (36). AS for intermediate risk PCa patients has increased over time. The rate of AS in NCCN favorable IRPCa patients increased from 13% to 45% from 2012 to 2020 (37). The 5-year treatment-free rate in AS patients was 73% for GG 1 disease and 57% for GG 2 disease. In these patients, delayed surgery resulted in 46% adverse pathology compared with immediate RP, but there was no difference in biochemical recurrence between the groups at short-term follow-up (37). A meta-analysis evaluating AS studies in IRPCa found that 10-year treatment-free survival was similar, but metastasis-free survival, cancer-specific survival, and OS were worse compared with LRPCa (38). Selected patients (only GG ≤2) had better metastasis-free survival (38). In the study, it was emphasized that unselected IRPCa patients experienced higher metastasis and cancer mortality compared to LRPCa patients; the importance of optimizing patient selection criteria in IRPCa was stated (38).

The EAU guidelines recommend that AS in IRPCa be offered with a weak recommendation to favorable patients with low-grade ISUP GG 2 (<10% pattern 4, PSA <10 ng/mL, ≤cT2a, low disease extent on imaging, and low extent of tumor in biopsies: ≤3 positive cores with GS 3+4 and ≤50% cancer involvement per core) who have a life expectancy of more than 10 years. Alternatively, it can be offered patients with another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, with an explanation of the increased potential risk of metastatic progression (11). The NCCN defines patients with GG 1 or 2, <50% biopsy cores positive, (e.g., <6 of 12 cores) and one intermediate risk factor (cT2b-cT2c, GG 2 or 3, PSA 10-20 ng/mL) as favorable IRPCa and recommends AS as an alternative to radical treatments (21). If AS is considered in favorable IRPCa patients, then especially patients with low percentage of 4 Gleason pattern, low tumor volume, low PSA density, and low genomic risk may be suitable (21).

As a result, AS will be an appropriate treatment for IRPCa patients. But we do not yet know exactly which IRPCa patients will be suitable for AS. It will be necessary to use different diagnostic methods for the selection of suitable IRPCa patients. The use of mpMRI may be beneficial in selecting appropriate IRPCa in the future.

Use of Multiparametric Prostate Magnetic Resonance Imaging in Active Surveillance Patients

mpMRI and mpMRI fusion biopsy increase the detection of clinically significant PCa in patients (39,40). Detection of clinically significant PCa in mpMRI fusion PB was shown to be statistically significantly higher (38% vs. 26%) (41). The use of mpMRI both in the first PB and follow-up biopsies in patients with previous negative biopsy increase detection of clinically significant PCa and it has been emphasized that prostate MRI can reduce the need for PB in patients (42). MRI-targeted biopsies detect more clinically significant PCa compared to standard PB (49.5% for systematic PB, 67% for targeted PB and 75.7% for targeted+systematic PB) (43). So, MRI-fusion biopsies are useful in detecting ISUP Grade 1 patients with higher accuracy. This will reduce the likelihood of detecting GS upgrade in AS follow-up. In a meta-analysis of 6 studies also showed that cancer upgrade (Gleason ≥3+4) was observed in 27% of patients when MRI-targeted + systematic biopsies were used (44). EAU guidelines recommend that mpMRI is performed prior to the initial PB or confirmation PB (11).

There are two important benefits of using mpMRI in AS. Initially, with the use of mpMRI before the first PB, the detection rate of clinically important PCa will increase. In one study, 10% of patients were found ineligible for AS according to the results of mpMRI-targeted PB compared to standard PB (45). In this way, patients will receive earlier diagnosis and treatment, and a more appropriate patient group will be selected for AS. This will increase the rate of success in AS. Secondly, it is thought that the use of prostate MRI in the follow-up of patients under AS can reduce the number of follow-up biopsies. It is also possible to use mpMRI in combination with other clinical information to detect clinically significant PCa. Based on PSA concentration, age, PI-RADS score, lesion length, and DRE findings, the Turkish Urooncology Association nomogram provides 75.6% sensitivity and 74.8% specificity in detecting clinically significant PCa in patients undergoing mpMRI fusion biopsy (46). The use of mpMRI may improve patient management and reduce unnecessary PB by contributing to the diagnosis of clinically significant PCa with high sensitivity and specificity. In recent years, follow-up protocols including mpMRI have also been used. Patients are selected using mpMRI-based selection criteria and follow-up protocols for some studies that have started in the past and are still ongoing (47).

It is thought that mpMRI may replace systemic repeat biopsies in the near future, but we need studies with a large patient cohort with long-term results. While mpMRI is a useful test in AS, it still cannot replace PB, and integration requires further research (48). In addition, ensuring optimal image quality in MRI, standardization of radiological findings in MRI and expertise in mpMRI reporting are crucial.

With the development of technology and increased accessibility, different diagnostic methods are increasingly used in PCa. One study reported that PSMA-PET-MRI improved the negative predictive value and sensitivity in the diagnosis of clinically significant PCa (49). The use of PSMA PET/CT may also improve patient selection for AS (50). However, these are clinical studies in small patient groups, and we need more data to make more precise comments on this issue (11).

Outcomes of Active Surveillance and Conversion to Treatment

AS is offered to patients as an alternative to RP and RT. The success rate is very high, especially in low-risk localized disease. In a study comparing patients with AS and those receiving curative treatment (RP or RT), no statistically significant difference was observed between 10-year CSS rates (<1% in all three groups); however, fewer disease metastases (<1% in all three groups) were observed in the treatment group (51). In another study, no difference was observed in the 10-year cumulative PCa mortality (AS 0.4% vs. RP 0.5%) between the treatment strategies (52). Outcomes from AS Protocols are shown in Table 2. Studies show that CSS and metastasis-free survival rates are

Table 2. Outcomes from active surveillance protocols

Authors reference	Article	Year	No curative treatment (%)	Median follow-up (years)	Disease specific survival (%)	Metastasis-free survival (%)	Overall survival (%)
Tosoian et al. (25)	Active surveillance program for prostate cancer: an update of the Johns Hopkins experience	2011	54	2.7	100	100	98.2
Bul et al. (12)	Active surveillance for low-risk prostate cancer worldwide: the PRIAS study	2013	75.6	1.6	100	2 cases	97.1 (2-years) 86.5 (4-years)
Selvadurai et al. (16)	Medium-term outcomes of active surveillance for localised prostate cancer	2013	68.8	5.7	96 (5-years)	2 cases	96 (5-years)
Tosoian et al. (6)	Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer	2015	63 (5 years) 50 (10 years) 43 (15 years)	5	99.9 (10 years) 99.9 (15 years)	99.4 (10 years) 99.4(15 years)	93 (10 years) 69 (15 years)
Klotz et al. (5)	Long-term follow-up of a large active surveillance cohort of patients with prostate cancer	2015	75.7 (5 years) 63.5 (10years) 55.0 (15years)	6.4	98.1 (10 years) 94.3 (15 years)	98.7	80 (10 years) 62 (15 years)
Godtman et al. (52)	Long-term results of active surveillance in the Göteborg randomized, population-based prostate cancer screening trial	2016	43	6.3	99.5 (10 years) 96 (15 years)	99 (10 years) 93 (15 years)	80 (10 years) 51 (15 years)
Tosoian et al. (4)	Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort	2020	48	5	99.9 (10 and 15 years)	99.9 (10 and 15 years)	93.2
Carlsson et al. (13)	Long-term outcomes of active surveillance for prostate cancer: the memorial sloan kettering cancer center experience	2020	58	15	100 (10 years)	99.4 (10 years)	94 (10 years)
Herden et al. (14)	Active surveillance for incidental (cT1a/b) prostate cancer: long-term outcomes of the prospective noninterventional HAROW study	2021	46.8	7.7	100	98.4	83.8

over 95% in patients under AS. Research indicates that AS is a safe and appropriate treatment approach in localized PCa. The risk of delaying patients' treatment is another concern. The EAU guidelines emphasize that for clinically localized low/intermediate-risk disease, no treatment modality is superior to another or to deferred active treatment (11).

CSS and OS are evidently good in eligible patients who are followed up in AS. Men can choose to stay in AS as long as they want, provided the disease remains stable, and life expectancy is over 10 years. However, it is known that more than one third of these patients require curative treatment due to Gleason upgrade, disease extent increase, disease stage, progression, or patient request (11). Different tests were used in the studies to evaluate the progression and stage of AS in the follow-up. The following tests include: PSA increase, PSA doubling time, PSA density, upgrade in repeat PB (reclassification), and DRE.

Progression of the disease in AS, and exclusion of the patient from the criteria for AS are the main reasons to recommend radical curative treatment (6). Crossing a PSA threshold, an increase in GG on repeat biopsy, or a change in T-stage findings on imaging or clinical examination is a reason for switching to active curative treatment during AS. In some studies, radical curative treatment was given to patients with a PSA doubling time of less than 3 years, GS upgrade (histologic reclassification) or clinical progression (5,53). It should not be overlooked that re-classification in PB and transition to radical curative treatment is more likely when patients have an increased number of positive cores and PSA density (12,54). In a meta-analysis, high PSA-D, >2 positive cores (in systematic biopsies), and African-American origin were found to be highly associated with re-classification (55). However, PSA kinetics alone are not sufficiently reliable in predicting adverse pathology and should not be used in place of annual biopsies in AS (56). Thus, in patients with elevated PSA alone or short PSA doubling time, it is recommended to make a decision by re-evaluation with repeat MRI and repeat biopsy instead of directly changing treatment (11).

The most common reason for patients to switch to active curative treatment is a GS upgrade (reclassification) during follow-up (21,25,53). Increase in tumor volume, a rise in PSA density, and patient anxiety are other factors (21). The stress of

living with cancer also creates a desire for treatment in patients. In a study involving the patients, it was shown that the most common reason (53%) for curative treatment was an increase in disease volume with GS upgrading (histologic reclassification) (57). In addition, curative treatment was given to 2% of patients for anxiety (57). After 10 years of follow-up, 41% of patients discontinued AS because of AS protocol-based reclassification, and 5% of patients discontinued AS due to anxiety or a patient request (47). In another study, 73.4% of the patients received curative treatment due to the AS protocol progression criteria and 8.9% because of anxiety (12). It should be kept in mind that providing psychological support to patients in AS may help reduce anxiety levels.

There is growing evidence that some gene mutations, for instance BRCA2 mutations, are more likely to be associated with aggressive cancer even when there is clinically LRPCa, so active treatment may be preferable to AS for these patients with genetic risk factors (58). In the near future, germline test results and findings of certain somatic mutations on biopsy tissue will determine the appropriate candidates for AS.

Conclusion

AS is an appropriate approach to protect patients from the side effects of curative treatments in PCa. It is recommended as an alternative to RP and radical RT with high survival rates in patients with LRPCa. AS is a safe and reasonable option for patients with clinically localized LRPCa. The NCCN guidelines even recommend it as the only treatment option in patients with vLRPCa. Data on AS in the IRPCa are limited. There is a need for studies with a large number of patients and long-term follow-ups on AS in IRPCa. AS may be preferred in the favorable IRPCa group. AS should be followed very carefully and the patients should be well informed about the risks in this group. mpMRI increases the detection of clinically important PCa. More appropriate patients are selected for AS with the use of mpMR. In addition, it is thought that the use of mpMRI may reduce the number of repeat prostate biopsies in follow-ups. However, there is no standard protocol for AS that includes prostate MRI. In light of future studies, it seems that mpMR-based follow-up protocols will be created. Also, genetic biomarkers will be used to select the most valid PCa patients for AS in the near future.

Ethics

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Footnotes

Authorship Contributions

Concept: G.Ö., Y.T., H.K.Ç., Design: G.Ö., Y.T., H.K.Ç., Data Collection or Processing: G.Ö., Y.T., H.K.Ç., Analysis or Interpretation: G.Ö., Y.T., H.K.Ç., Literature Search: G.Ö., Y.T., H.K.Ç., Writing: G.Ö., Y.T., H.K.Ç.

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